Levodopa drugs

- levodopa (Brocadopa, Larodopa) up to 1 g six times a day, Levodopa with a dopadecarboxylase inhibitor:
- levodopa with benserazide (Madopar) up to 800 mg of levodopa with 200 mg benserazide, daily in divided doses,
- levodopa with carbidopa (Sinemet) up to 1.5 g of levodopa with 150 mg carbidopa, daily in divided doses.

Other drugs

- amantadine (Symmetrel) up to 100 mg twice a day,
- bromocriptine (Parlodel) up to 20 mg three times a day,
- selegiline (Eldepryl) up to 5-10 mg once daily.

The actions of bromocriptine and selegiline are dopaminergic and hence may exacerbate the unwanted effects of levodopa drugs.

(3) "Adjust dose" as used on the algorithm means adjust the dose to give the minimum dose needed to produce the maximum benefit with the minimum unwanted effects. It is rarely necessary to give therapy urgently, and the medication should therefore be started in small doses and increased slowly as the effect of each change is noted. If appreciable unwanted effects occur before there is any improvement the medication should be stopped. If unwanted effects and improvement occur simultaneously then careful adjust-

ment is necessary, and this may take several weeks and require repeated visits to a doctor. Of course, when there is adequate improvement the dose should not be further increased. It is rarely reasonable to attempt to remove all symptoms and signs, as this is usually impossible except in very mild disease. The aim should be for the patient to be able to lead a normal life. The benefits of anticholinergic drugs do not change much hour by hour or year by year. With the levodopa drugs, however, the unwanted effects increase the longer they are used, especially with high doses. Therefore the dose should be kept as small as possible and the patient discouraged from increasing the dose. The patient should be advised to take a small dose when he or she is doing less and needs less. If the on-off phenomenon or rapid deterioration occurs at a constant interval after a dose smaller doses given more frequently are often better than increasing the total dose.

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Medical History

A D Waller and the electrocardiogram, 1887

A H SYKES

This year is the centenary of the first recorded electrocardiogram. The paper in which A D Waller announced his discovery led directly to the work of Willem Einthoven, Sir Thomas Lewis, and others and so to the establishment of electrocardiography in clinical medicine.¹ It is, therefore, appropriate to recall Waller's achievement at this time.

A physiologist's son

Augustus Desiré Waller (1856-1922) was the only son of Augustus Volney Waller (1816-70), who made many important contributions to physiology including the eponymous degeneration of neurones following transection. A D Waller qualified in medicine at Aberdeen in 1878, but from the outset he was determined to emulate his father as a physiologist. He worked briefly with Ludwig in Leipzig and with Chauveau in Lyons (he was born in Paris and spent much of his boyhood in Europe, becoming fluent in French and German) and then with Burdon-Sanderson in the department of physiology at University College London. He spent a short time teaching physiology at the Royal Free Hospital School of Medicine and then for 18 years was lecturer in charge of physiology at St Mary's Hospital Medical School where his work on the electrocardiogram was undertaken. In 1902 he left to become

the first and only director of the physiological laboratory at the University of London situated in the former Imperial Institute, which was then the headquarters of the university. He was elected FRS in 1892 at the age of 35, the same age as his father had been on election. He was appointed professor in 1912 and received many awards in Britain and abroad (fig 1).

He and his wife and family lived a full life which revolved around his career as a physiologist. He had a laboratory at his spacious home in St John's Wood where he was helped by his wife, a former medical student. His children, his guests, and his pet bulldogs were often the subjects for his experiments, and it was one of his bulldogs, Jimmie, that was the subject of a now famous parliamentary question in 1909.² Visiting scientists were entertained, and there were family expeditions, frequently in the newly invented motorcar, to attend scientific conferences. A proposed visit to Einthoven in Leiden one winter was preceded by a telegram: "How is the skating?" He enjoyed giving popular lectures and was something of a showman, but his energy and enthusiasm were devoted to his chosen science and to the University of London. There are a few brief biographies,^{3,4} but his personality is elusive and he left few personal papers to help any serious biographer.

Capillary electrometer

There were several forerunners to Waller in cardiac electrophysiology. The action current of the exposed frog heart had already been demonstrated by the use of relatively insensitive instruments, but the advent of Lippman's capillary electrometer in 1872 marked a great advance in speed and sensitivity. It was first used to record the electrical activity of the exposed heart of the frog by Marey in 1876.⁵ It was taken up by Burdon-Sanderson for his wide ranging studies of electrophysiology including the heart.⁶ This

was at the time when Waller had started working at University College, where he became familiar with the technique and applied it to the exposed heart of mammals.⁷

It was Waller's scientific imagination that led him to realise that cardiac potentials could pass through the chest wall and so be detected by a suitable measuring instrument; it was his technical skill that first demonstrated the existence and the nature of these electrical signs of cardiac activity in intact man and animals. He recorded the regular fluctuations of the mercury meniscus of a capillary electrometer when attached to man by electrodes consisting of jars of saline, in which hands or feet were immersed, or by metal electrodes (a silver teaspoon) in the mouth. He also recorded the movement of the heart by means of a lever and showed that the electrical events occurred in time with but slightly ahead of the mechanical events. He

FIG 1—A D Waller in Court dress 1912. (Courtesy of Carol Cheesbrough.)

was concerned lest the movement of the electrode over the heart, by interrupting the circuit, might have produced deflections which would therefore be only artefacts. He also guarded against this by the use of electrodes made from saline soaked pads which were less likely to move.

From his examination of the responses from different combinations of electrodes, from hands, feet, and chest, he showed clearly the asymmetrical nature of the electrocardiogram. Those leads that gave marked deflections he called "favourable"; they included leads I and II, but lead III was found by Waller to be "unfavourable." The size and form of the electrocardiogram were recorded photographically, the plate being moved across a light beam which cast a shadow of the moving mercury meniscus. The plate was carried on a toy railway wagon running on rails; this is now in the keeping of the Science Museum, London. The electrocardiogram as first recorded by Waller (fig 2) bears little relation to its well known form today, but it was, incontrovertibly, a manifestation of the periodical electrical activity of the heart obtained by non-invasive means.

Prompted, perhaps, by his medical training, Waller went to some trouble to find a case of situs inversus viscerum to demonstrate, as he predicted, the reversal of the asymmetry of the electrocardiogram. Thus the normal lead II now became unfavourable and the formerly unfavourable left hand-right foot lead became favourable. This was a neat confirmation of Waller's view

that the asymmetry arose as a consequence of the electrical fields spreading from a source, the contracting heart, which was situated at an angle to one side of the midline, as depicted in his diagram (fig 3).

Waller had joined that distinguished group of physiologists who had written their own textbook, and he was able to include in it an illustration of the electrocardiogram, its first appearance in a teaching text.⁸

FIG 2—Enlargement of a single systole. Upper line: cardiometer; lower line: electrometer. From *Philos Trans R Soc Lond (Biol)* 1889;180:190. (Courtesy of Royal Society.)

FIG 3—The electrical fields of the heart according to Waller. Broken lines (a—a) represent equipotential lines surrounding apex (A); solid lines (b—b) represent equipotential lines surrounding base (B); dotted lines (c—c) represent current flow. From *Philos Trans R Soc Lond (Biol)* 1889;180:186. (Courtesy of Royal Society.)

Enter Einthoven

Perhaps more important than anything he did subsequently on the electrocardiogram, he indirectly advanced electrocardiography profoundly by introducing Einthoven to this subject, an introduction gratefully and gracefully acknowledged by Einthoven at the now famous meeting of the Chelsea Clinical Society in 1912.⁹ According to Waller,¹⁰ "The first experiment was made in the St Mary's laboratory in May 1887 and demonstrated there to many physiologists, among others to my friend Prof Einthoven of Leiden"¹⁰; (I have been unable to find independent confirmation of this occasion).

Waller's first paper was followed by a longer one in the *Philosophical*

*Transactions of the Royal Society*¹¹ and by a number of shorter communications to societies. A special meeting of the Berlin Physiological Society was called in his honour in 1889 at which he demonstrated the electrocardiograph on a large dog, on a horse in the courtyard outside connected by extra long recording leads, and on Emil du Bois Reymond, the doyen of electrophysiologists.

After 1890 he deserted electrocardiography and returned to it only in 1909 after Einthoven had developed the string galvanometer. His renewed interest did not lead to any findings of great importance, although he did much to popularise what had now become Einthoven's subject. He tried desperately hard to obtain a string galvanometer from Einthoven but without success since the latter had a carefully planned programme of work for his instruments, but he kept in touch with its commercial development by the Cambridge Scientific Instrument Company. Eventually he acquired one himself, but from where exactly is not known since it is not in the numbered list of the first purchasers¹²; it may have been an Edelman model from Germany. Nevertheless, it is said that in 1908 he had at the university laboratory of physiology the only string galvanometer available for clinical use in England,¹³ and it was with this instrument that Lewis, at the start of his career, made his first electrocardiographic recordings.¹⁴

Nevertheless, it is Einthoven who is remembered as the pioneer of electrocardiography; Waller appears in a few historical articles only, and even there his achievements are overshadowed by those who worked after him. This is perhaps a reflection of what he failed to do in his original investigations as much as by what he could not have done because he did not have the techniques which became available only later. For example, for a time Waller wrongly believed that the cardiac impulse travelled from apex to base, a view which was corrected in 1892 by Bayliss and Starling,¹⁵ who otherwise confirmed Waller's findings. The quality of his electrometer recordings was not good; there was no evident atrial component but only a small biphasic deflection which corresponds to the QRS wave. The capillary electrometer was a sluggish instrument with a great deal of inertia, and it did not reproduce faithfully the rapid changes in potential of the electrocardiograms.

This problem had, however, been appreciated by the physicist GJ Burch of Oxford who devised an arithmetical method of correcting the observed fluctuations of the electrometer to show the true pattern. He worked in collaboration with Burdon-Sanderson, who applied the correction to the electrophysiology of skeletal muscle. Burch did not publish his method until 1890,¹⁶ but he had used it earlier and since Burch, Burdon-Sanderson, and Waller were members of the then small Physiological Society it is unlikely that Waller did not know about it. Why then did he not apply it to his own results either at the time or three years later when Burch had published? Had he done so he would have gained much more recognition for his work. But it was his friend Einthoven who a few years later demonstrated the true wave form of the electrocardiogram.¹⁷ Einthoven also used the capillary electrometer for this work, the string galvanometer was still a few years away (1903), and he developed a method of correction independently of Burch. This description of the electrocardiogram and the use of the PQRST nomenclature has now become classical.

Waller was not the first to use the term "electrocardiogram," and it does not appear in any of his earlier writings. The mechanical registration of the heart he called a cardiogram, and the electrical variations were referred to as the electrometer or electrometer line. Einthoven appears to have been the first to speak of the electrocardiogram, although he generously, but wrongly, ascribed it to Waller at the Chelsea meeting.⁹ Finally, Waller has been criticised for his failure to foresee the clinical importance of the electrocardiogram. He expressed no views on the matter at the time of his original work, only later (1908) when the string galvanometer was becoming better known. He must have changed his opinion, for subsequently he became a consultant to the National Heart Hospital and undertook the routine examination of army recruits during the war years.

Uncovering basic truths

Waller's apparent indifference to the clinical importance of the electrocardiogram may have arisen from his conception of the role of the physiologist since he was, in fact, conscious of the importance of physiology to medicine. In a series of lectures he published, under the title *Physiology the Servant of Medicine*,¹⁸ he acknowledged that medical progress was the ultimate purpose of physiology: [It is] "my conviction that while it is essential that scientific inquiry should be pursued for its own sake without regard to immediate utility its ultimate justification consists in its practical application to the service of Mankind." But by this he meant that the physiologist should uncover basic truths in the laboratory which others would then take up and develop in the hospital. In his own work he strived

after insights into the basic properties of cells and organs through his investigations of the electrical activity of nerve, skin, glands, the eye, and even germinating seeds. This attitude is well expressed in the dedication to his father in his textbook⁸:

A V Waller: Emigration of leucocytes: degeneration and regeneration of nerves: cilio-spinal region: vasoconstrictor action of sympathetic.

These were bold, new discoveries opening up hitherto unknown aspects of physiology to medicine. This is what Waller hoped to achieve and the discovery of the electrocardiogram is surely such an achievement.

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A young married woman has had a malignant melanoma excised from her right calf. There is no evidence of secondary spread. She has a 1 year old child. What advice should be given about further pregnancy, and is it safe for her to continue using a combined pill? What is the prognosis for this woman?

Reproductive factors influence the incidence of malignant melanoma, and isolated case reports have suggested that pregnancy may have an adverse effect on the progress of the disease.¹ Nevertheless, women who become pregnant after developing malignant melanoma have the same survival rate as those who do not.² There is at present no way of identifying women who may be at risk of recurrence related to pregnancy.² Ideally, this patient should be told that recurrences during pregnancy have been reported but because these may be coincidental she should not be advised to avoid pregnancy. There is no epidemiological reason for advising her to wait a certain period before conceiving, though it would seem wise to wait until another two or three years have passed without any sign of recurrence. The question of a link between oral contraceptives and malignant melanoma is debatable, but recent large surveys have shown no increase in the incidence of melanoma among pill users.^{3,4} Oral contraceptives are therefore not contraindicated, but because some reports have suggested a link the woman may feel happier using a non-hormonal method. Her prognosis depends on several factors, such as the thickness of the lesion and its histological appearance.⁵ Overall five year survival rates vary between 30% and 95%. Women have a better survival rate than men, and other favourable features for this woman are her young age and the fact that the lesion was on a limb.⁵—JAMES OWEN DRIFE, senior lecturer in obstetrics and gynaecology, Leicester.

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