

# SUXAMETHONIUM – THE DEVELOPMENT OF A MODERN DRUG FROM 1906 TO THE PRESENT DAY\*

by

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## 1. INTRODUCTION

ON INITIAL impression, suxamethonium contrasts sharply with drugs such as digitalis or quinine in having a short, and fairly straightforward history. In fact, its emergence as a therapeutically useful drug was surprisingly long and complex.

Suxamethonium (also known as succinylcholine, succinylidicholine) is a neuromuscular blocking agent, commonly classed as a “depolarizing agent”. It blocks transmission of impulses from motor nerves to skeletal muscle by interacting with receptors on the post-junctional membrane. These motor end-plate receptors normally combine with the transmitter molecule, acetylcholine, which is released from the nerve terminal on the arrival of an action potential. Acetylcholine is synthesized and stored in the nerve terminal. Its release results from nerve terminal depolarization, and depends on the entry of calcium ions. The transmitter molecules diffuse across the neuromuscular junction and interact with motor end-plate receptors causing a depolarization of the end-plate, which is enough to initiate electrical changes leading to muscle contraction.

Suxamethonium is structurally similar enough to acetylcholine to cause a membrane depolarization, and a muscle twitch, after which blockade sets in. Views of its mechanism of action have changed as the understanding of neuromuscular transmission has progressed.

## 2. CURARE – AN IMPORTANT COMPETITIVE NEUROMUSCULAR BLOCKING AGENT

The history of neuromuscular blocking agents starts with curare,<sup>1</sup> a substance which Koelle calls “a drug with a long and romantic history”.<sup>2</sup> Curare, a complex

\* Dedicated to Professor W. Feldberg on the occasion of his eightieth birthday.

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<sup>1</sup> The early literature on curare is very large, e.g.: A. R. McIntyre, *Curare: its history, nature, and clinical use*, University of Chicago Press, 1947; Philip Smith, *Arrows of mercy*, Toronto, Doubleday, 1969; K. Bryn Thomas, *Curare – its history and usage*, London, Pitman Medical, 1964; also in Lloyd G. Stevenson, *The meaning of poison*, Lawrence, University of Kansas Press, 1959. A bibliography of the older literature is: Instituto Brasileiro de Bibliografia e Documentacao, *Curare – a bibliography*, Rio de Janeiro, Conselho Nacional de Pesquisas, 1957.

<sup>2</sup> George B. Koelle, ‘Neuromuscular blocking agents’, in Louis S. Goodman and Alfred Gilman (editors), *The pharmacological basis of therapeutics*, 5th ed., New York, Macmillan, 1975, pp. 575–588.

group of competitive neuromuscular blocking agents, has been used for centuries to kill wild animals by tribes in South America, Borneo, and other aboriginal cultures. It is prepared as a crude extract of one or more of a variety of plants. In eastern Amazonia, the principal sources are various species of *Strychnos*, while the natives of western Amazonia use *Chondrodendron* species. When a dart coated with curare hits an animal, its skin is penetrated, the drug enters the circulation, and death due to paralysis of the respiratory muscles promptly ensues. The advantage of curare is that it is poorly absorbed through the gut wall of persons eating meat killed in this way – it is thus a very specific poison.

Curare was known to western medicine in the nineteenth century. McIntyre,<sup>3</sup> surveying its clinical history, pointed out that its use in the treatment of tetanus was first suggested by Sir Benjamin Collins Brodie (1783–1862)<sup>4</sup> in a letter to Pierre Flourens in 1811, also reporting his recent demonstration that curarized animals could be resuscitated with artificial respiration.<sup>5</sup> In 1858, Lewis Albert Sayre (1820–1900) first used curare in human tetanus – unfortunately the patient, an Irish labourer in New York, died.<sup>6</sup> Over the next forty years, the use of curare in tetanus became widespread, and epilepsy, hydrophobia, and chorea were similarly treated. Claude Bernard (1813–1878) described the drug's neuromuscular blocking action in 1856,<sup>7</sup> having worked with it since 1844.<sup>8</sup>

Modern clinical use of curare began in 1932, when Ranyard West<sup>9</sup> employed curare-based preparations in the treatment of tetanus and spastic disorders. However, it was the introduction of electric shock therapy (ECT) for the treatment of depressive illness that was to provide the main impetus for curare's widespread use. Indeed, the entire ECT technique would have been abandoned had not an American psychiatrist, Abram Elting Bennett (b. 1898), advanced the idea of using curare to block neuromuscular transmission, thus preventing the disturbing occurrence of fractures and dislocations due to massive contraction of skeletal muscles during treatment.<sup>10,11</sup>

<sup>3</sup> McIntyre, op. cit., note 1 above, pp. 182–208.

<sup>4</sup> Sir Benjamin Collins Brodie (the elder), the distinguished surgeon and physiologist, was the first surgeon to be elected President of the Royal Society. Biographical sources include: Charles Hawkins (editor), *The works of Sir Benjamin Collins Brodie, with an autobiography*, 3 vols., London, Longman Green, 1865; Timothy Holmes, *Sir Benjamin Collins Brodie*, London, Fisher Unwin, 1898; W. R. LeFanu, 'Sir Benjamin Brodie FRS (1783–1862)', *Notes Rec. R. Soc. Lond.*, 1964, 19: 42–52; [Obituary], *Lancet*, 1862, ii: 452–457, 482–483, 492, 521–522; K. Bryn Thomas, 'Benjamin Brodie: physiologist', *Med. Hist.*, 1964, 8: 286–291.

<sup>5</sup> This letter, reported by Dieu in 1863, had been reproduced in *Union méd. Paris*, 1859, 4: 98. (A. Dieu, *Histoire du curare*, Strasbourg, 1863.)

<sup>6</sup> L. A. Sayre, 'Two cases of traumatic tetanus', *N.Y. J. Med.*, 1858, 4: 250–253. Sayre was an eminent American orthopaedic surgeon. His major contributions include the introduction of the plaster of Paris jacket for treatment of tuberculosis of the spine. See Alfred R. Shands jr., 'Lewis Albert Sayre, the first professor of orthopaedic surgery in the U.S.', *Curr. Pract. orthopaedic. Surg.*, 1969, 4: 22–42.

<sup>7</sup> Claude Bernard, 'Analyse physiologique des propriétés des systèmes musculaire et nerveux au moyen de curare', *C.r. hebd. Séanc. Acad. Sci., Paris*, 1856, 43: 825–829.

<sup>8</sup> Thomas, op. cit., note 1 above, p. 62.

<sup>9</sup> Ranyard West, 'Curare in man', *Proc. R. Soc. Med.*, 1932, 25: 1107–1116.

<sup>10</sup> Details of Bennett's life and work, including his work on curare, are given in his autobiography, *Fifty years in neurology and psychiatry*, New York and London, Intercontinental Medical Book Corp., 1972.

<sup>11</sup> A. E. Bennett, 'How "Indian arrow poison" curare became a useful drug', *Archos. Neurobiol. (Madr.)*, 1965, 28: 606–620.

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Bennett and his colleagues at the Lincoln, Nebraska, Orthopedic Hospital first produced temporary muscle relaxation in children with spastic paralysis. In 1940, they successfully used curare in ECT for the first time, and it is due to the availability of neuromuscular blocking agents that ECT is still in use today.<sup>12,13</sup> This success led Bennett to suggest to Lewis H. Wright of the American pharmaceutical company, E. R. Squibb & Sons, that curare could usefully produce muscle relaxation during general anaesthesia.<sup>14</sup> The company had considerable experience in working with curare: in 1938, Richard C. Gill, an American who had explored and worked in Ecuador, brought back the largest amount of field-test curare so far gathered by an outsider, and made this available to the Squibb research department.<sup>15</sup> In 1940, this laboratory prepared a standardized curare extract called "Intocostrin".<sup>16</sup> Wright discussed the matter with a Montreal anaesthesiologist, Harold R. Griffith (b. 1894),<sup>17</sup> who in 1942 carried out the first clinical trials of curare as a muscle relaxant on some twenty-five patients.<sup>18</sup>

A major problem with curare was difficulty of supply, for its availability limited the extent of its investigation and exploitation. It was this, coupled with problems related to the wide diversity seen in composition and neuromuscular blocking strength of the various samples of curare collected, that stimulated work to find synthetic chemicals with curariform action.

Over seventy years before the introduction of "Intocostrin", work had been done by Alexander Crum Brown (1838–1922) and Thomas Richard Fraser (1841–1920) on the pharmacological actions of quaternary salts. [A quaternary ammonium compound is one in which all four hydrogen atoms of the ammonium ion ( $\text{NH}_4^+$ ) have been substituted by organic (carbon-containing) radicals.] Crum Brown and Fraser were interested in the relationship between the chemical structure of a compound and its biological activity.<sup>19</sup> They showed that a pharmacologically diverse group, the

<sup>12</sup> The continued use of ECT in the treatment of depressive illness is still problematic. The procedure is currently being evaluated by clinical trials.

<sup>13</sup> A. E. Bennett, 'Curare: a preventive of traumatic complications in convulsive shock therapy', *Am. J. Psychiat.*, 1941, **97**: 1040–1060; *idem*, 'Preventing traumatic complications in convulsive shock therapy by curare', *J. Am. med. Ass.*, 1940, **114**: 322–324.

<sup>14</sup> *Idem*, 'The history of the introduction of curare into medicine', *Anesth. Analg. curr. Res.*, 1968, **47**: 484–492.

<sup>15</sup> Bennett, *op. cit.*, note 10 above.

<sup>16</sup> O. Wintersteiner and J. D. Dutcher, 'Curare alkaloids from *Chondrodendron tomentosum*', *Science*, 1943, **97**: 467–470.

<sup>17</sup> Griffith subsequently became professor of anaesthesia at McGill University. An autobiographical account is: H. R. Griffith, 'An anaesthetist's valediction', *Can. Anaesth. Soc. J.*, 1967, **14**: 373–381.

<sup>18</sup> H. R. Griffith and G. E. Johnson, 'The use of curare in general anaesthesia', *Anesthesiology*, 1942, **3**: 418–420.

<sup>19</sup> The investigations of Crum Brown and Fraser form a link in a chain of enquiry that continues to this day. They were awarded the Makkdougall Brisbane Prize of the Royal Society of Edinburgh (1866–68) for this work. Neuromuscular blocking agents have featured repeatedly in studies of the relationship between chemical constitution and biological activity and have been used in most of the theoretical models of drug/receptor interaction. See: William F. Bynum, 'Chemical structure and pharmacological action: a chapter in the history of nineteenth-century molecular pharmacology', *Bull. Hist. Med.*, 1970, **44**: 518–538; John Parascandola, 'Structure-activity relationships – the early mirage', *Pharm. Hist.*, 1971, **13**: 3–10; *idem*, 'The controversy over structure-activity relationships in the early twentieth century', *ibid.*, 1974, **16**: 54–63.

alkaloids, if converted to quaternary salts, all lost their diversity of action, each acquiring the neuromuscular blocking properties of curare.<sup>20</sup> They were responsible for producing the first synthetic curariform substances, "readily obtained in a state of perfect purity, and therefore, of constant strength".<sup>21,22,23</sup>

Crude curare is a very complex mixture of many different alkaloids. The next step in the development of neuromuscular blocking agents was the attempt to extract and purify individual components of curare, with a view to determining their chemical structure. One such component is *d*-tubocurarine. The pure alkaloid was isolated and extracted from a small bush plant, *Chondrodendron tomentosum*, a known source of curare, by Harold King (1887–1956), an organic chemist working at the National Institute for Medical Research (NIMR) in Hampstead. It was a very difficult task, involving a complex method of extraction, using first ether and then chloroform. Nonetheless, King was able in 1935 to publish the chemical structure he had determined for *d*-tubocurarine.<sup>24</sup> The alkaloid was called "tubocurarine" because it was a component in a type of crude curare classified by Boehm as tube curare – a reference to the bamboo tubes used by South American Indians to store this type of curare.<sup>25</sup>

The structure that King had worked out for *d*-tubocurarine was that of a large, relatively rigid molecule, containing two quaternary ammonium groups, at opposite ends of the molecule (Fig. 1a). King's chemical characterization of *d*-tubocurarine marked the start of a period of rapid advance in neuromuscular pharmacology, and enabled synthetic chemists and pharmacologists to start work on making simpler molecules with properties similar to those of curare. Some years later, Harington (director of the NIMR) commented, "It was however the work of King on the curare alkaloids which I think really opened up the way to the systematic pharmacological work that has proved so profitable. King's research on curare was a masterly series of investigations extending over many years, and leading from the isolation of *d*-tubocurarine in the pure state to the determination of the constitution of this alkaloid".<sup>26,27</sup>

<sup>20</sup> Thomas, *op. cit.*, note 1 above, p. 77.

<sup>21</sup> A. Crum Brown and T. R. Fraser, 'On the connection between chemical constitution and physiological action. Part I. On the physiological action of the salts of the ammonium bases derived from strychnia, brucia, thebaia, codeia, morphia, and nicotia', *Trans. R. Soc. Edinb.*, 1868, **25**: 151–203.

<sup>22</sup> Crum Brown and Fraser reported further work in 'On the connection between chemical constitution and physiological action. Part II. On the physiological action of the ammonium bases derived from atropia and conia', *ibid.*, 1869, **25**: 693–739.

<sup>23</sup> Crum Brown trained in medicine at Edinburgh University, and subsequently became interested in organic chemistry. Biographical accounts include: [Obituary], *J. chem. Soc.*, 1923, **123**: 3422–3431; D. C. Goodman, 'Alexander Crum Brown', in C. C. Gillispie (editor), *Dictionary of scientific biography*, vol. 2, New York, Charles Scribner's Sons, 1970, pp. 514–516; D. F. Larder, 'Alexander Crum Brown and his doctoral thesis of 1861', *Ambix*, 1967, **14**: 112–132.

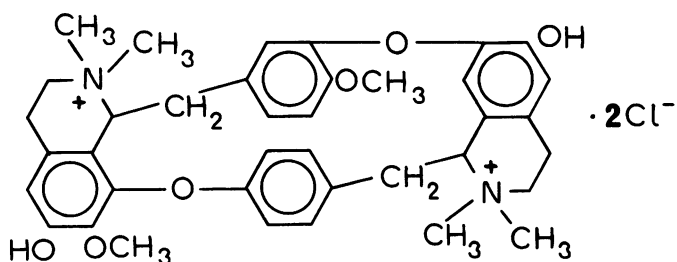
Fraser, also a medical graduate of Edinburgh, was professor of materia medica there from 1877 to 1918. He was elected FRS in 1877, and knighted in 1902. See: [Obituary], *Br. med. J.*, 1920, **i**: 100–101; [Obituary], *Proc. R. Soc. Lond.*, 1921, **92B**: xi–xvii.

<sup>24</sup> H. King, 'Curare alkaloids. Part I – tubocurarine', *J. chem. Soc.*, 1935, 1381–1389.

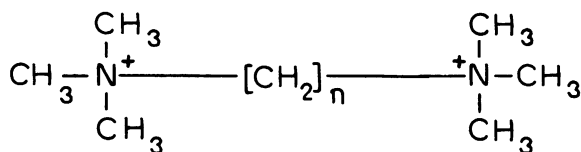
<sup>25</sup> It has since become clear that the method of storage used for curare is not related to its chemical structure – any of the various curare alkaloids might be present in any type of container.

<sup>26</sup> Charles Harington, 'Opening remarks', in M. Harington (editor), *Hypotensive drugs: proceedings of a*

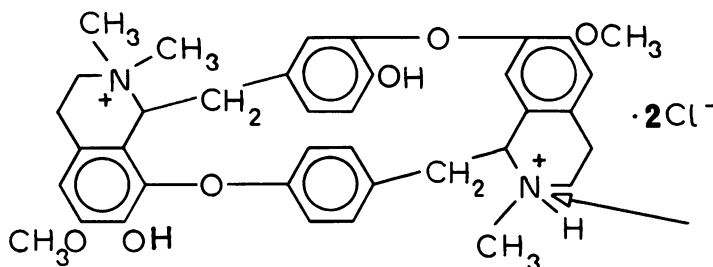
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(a)



(b)



(c)

Figure 1.

(a) King's initial structure for *d*-tubocurarine (chloride). Two quaternary nitrogen atoms are present.

(b) General chemical formula for members of the methonium series. The structure (Polymethylene bis-trimethyl ammonium) can incorporate a variable number (*n*.) of methylene (–CH<sub>2</sub>–) groups, allowing varying degrees of separation of the two positively charged, quaternary nitrogen atoms.

(c) Revised structure for *d*-tubocurarine (chloride). The positions of the hydroxyl groups were modified by King, Everett *et al.*,<sup>64</sup> who showed that one of the nitrogen atoms (arrow) was not quaternary.

*symposium on hypotensive drugs and the control of vascular tone in hypertension*, London and New York, Pergamon Press, 1956, pp. 1–3.

<sup>27</sup> Harold King, an outstanding organic chemist, was made FRS in 1933. The most informative obituary is: C. Harington, 'Harold King, 1887–1956', *Biogr. Mem. Fellows R. Soc. Lond.*, 1956, 2: 157–171. Other obituaries include: *Nature, Lond.*, 1956, 177: 604–605; *Br. med. J.*, 1956, i: 521–522, 578.

During the 1930s, the NIMR was a world centre of pharmacological research. Henry Hallett Dale (1875–1968) had gone there in 1914, and from 1928 to 1942 was Director of the Institute. However, he maintained his active research interests and his laboratory attracted many distinguished physiologists and pharmacologists, including Wilhelm Feldberg (b. 1900), J. H. Gaddum (1900–1965), Marthe Vogt (b. 1903), and G. L. Brown (1903–1971). There can be little doubt that King's interest in the curare alkaloids was stimulated by the work of Dale and his colleagues on the chemical transmission of nerve impulses at the neuromuscular junction. The years 1933–36 were ones of outstanding progress in Dale's group, with some twenty-four papers published in the *Journal of Physiology* on the transmitter role of acetylcholine at the neuromuscular junction, autonomic ganglia, and a variety of other sites.<sup>28</sup> Clearly, knowledge of the structure of a substance which blocked neuromuscular transmission was of considerable importance. However, King's interest in alkaloids began much earlier, before he joined the NIMR. In 1912, he worked at the Wellcome Physiological Laboratories, then under Dale's direction. King then moved to the Wellcome Chemical Laboratories at Dartford. There, in the laboratory of Frank Lee Pyman, his studies on alkaloids began with the isolation of l-hyoscyne, and the resolution of hyoscyne and its components, oscine and tropic acid. He joined the Medical Research Council shortly after the end of World War I, which brought him back into contact with Dale.<sup>29</sup> He remained with the MRC for thirty-one years, until his retirement in 1950. As we shall see, the Hampstead laboratory produced one of the major contributions to the methonium compounds over a decade later.

### 3. THE METHONIUM COMPOUNDS

Progress on synthetic curare substitutes was delayed by the outbreak of World War II four years after the publication of King's first paper on curare alkaloids. However, by the late 1940s, interesting compounds began to appear. Many workers tried to synthesize structures related to, but less complicated than *d*-tubocurarine,<sup>30</sup> and a few groups chose to make molecules containing two quaternary nitrogen atoms. In 1948, two groups of British workers, Barlow and Ing<sup>31</sup> and Paton and Zaimis,<sup>32</sup> reported work on a family of compounds characterized by such a *bis*-quaternary structure (Fig. 1b).

Barlow and Ing based their work on the imitation of the *bis*-quaternary structure of

<sup>28</sup> A fascinating and authoritative eyewitness account of this period can be found in: Wilhelm Feldberg, 'The early history of synaptic and neuromuscular transmission by acetylcholine: reminiscences of an eye witness', in *The pursuit of nature. Informal essays on the history of physiology*, Cambridge University Press, 1977, pp. 65–83.

<sup>29</sup> The influence of Dale on King's work is assessed in Harington, *op. cit.*, note 26 above. King appears to have written little other than his scientific papers – no evidence about the origin of his interests could be found in the NIMR archives.

<sup>30</sup> Koelle, *op. cit.*, note 2 above, p. 575.

<sup>31</sup> R. B. Barlow, and H. R. Ing, 'Curare-like action of polymethylene *bis*-quaternary ammonium salts', *Nature, Lond.*, 1948, **161**: 718.

<sup>32</sup> W. D. M. Paton and E. J. Zaimis, 'Curare-like action of polymethylene *bis*-quaternary ammonium salts', *ibid.*, 718–719.

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curare.<sup>33,34</sup> William D. M. Paton (b. 1917) and Eleanor Zaimis (b. 1915) were at NIMR, Hampstead; not, in fact, studying neuromuscular blocking compounds, but drugs that cause histamine release. Paton's observation of slight, but definite, respiratory arrest with a member of another set of histamine releasing dibasic compounds<sup>35</sup> alerted him to a pharmacological action at the neuromuscular junction, and on studying the diquaternary compound of the formula shown in Fig. 1b, where  $n = 8$ , the principal action seen was one of respiratory arrest. In a subsequent paper, Paton and Zaimis said, "Our attention was drawn to the [methonium] series during a test of the power of the octamethylene compound to liberate histamine".<sup>36</sup> They therefore discovered the series as a result of careful observation in experimental work: unlike Barlow and Ing, they did not approach the problem from a theoretical basis starting with the structure of *d*-tubocurarine.

Why did Barlow and Ing become interested in these diquaternary compounds? The answer can be found with Ing's long-standing interest in the relationship between chemical structure and biological activity. While at the Pharmacology Department of University College London, with Winifred Wright during the late 1920s and early 1930s, Ing had worked on the curariform action of onium salts, such as those of tetramethylammonium ( $[\text{CH}_3]_4\text{N}^+$ ), tetramethylphosphonium ( $[\text{CH}_3]_4\text{P}^+$ ), and trimethylsulphonium ( $[\text{CH}_3]_3\text{S}^+$ ).<sup>37</sup> By the 1940s, he had come to the view that the powerful curare-like activity of tubocurarine might be due to the presence of two quaternary groups at some optimal distance apart in the molecule. It was for this reason that he set out to imitate the structure of *d*-tubocurarine.<sup>38</sup>

These compounds became known as the methonium series, and one of them, decamethonium, was found to be a valuable depolarizing agent. The series also included hexamethonium, a ganglion blocking drug which became important in the treatment of hypertension.<sup>39</sup> The synthesis of the methonium compounds, and the

<sup>33</sup> R. B. Barlow, 'The synthesis and pharmacological properties of *bis*-onium salts', B.Sc. thesis, Oxford University, 1949.

Richard Barlow (b. 1925) was a research student at Oxford working for the degree of B.Sc., with Harry Raymond Ing (1899–1974) as his supervisor.

<sup>34</sup> Ing, by training an organic chemist, was an eminent "chemical pharmacologist". He became FRS in 1951. See H. O. Schild and F. L. Rose, 'Harry Raymond Ing, 1899–1974', *Biogr. Mem. Fellows R. Soc. Lond.*, 1976, 22: 239–255.

<sup>35</sup> W. D. M. Paton, personal communication, 1978.

<sup>36</sup> W. D. M. Paton and E. J. Zaimis, 'The pharmacological actions of polymethylene *bis*-trimethylammonium salts', *Br. J. Pharmac. Chemother.*, 1949, 4: 381–400.

<sup>37</sup> Accounts of this work can be found in: H. R. Ing and W. M. Wright, 'The curariform action of quaternary ammonium salts', *Proc. R. Soc. Lond.*, 1931, 109B: 337–353; *idem*, 'Further studies on the pharmacological properties of onium salts', *ibid.*, 1933, 114B: 48–63; H. R. Ing, 'The curariform action of onium salts', *Physiol. Rev.*, 1936, 16: 527–544.

<sup>38</sup> Ing was a friend of King, and well aware of his work. In his lectures on chemical pharmacology at Oxford, Ing used to show his students how, in both decamethonium and *d*-tubocurarine, ten atoms separated the two quaternary nitrogen atoms, suggesting the existence of an optimal separation for neuromuscular block. (Barlow, personal communication, 1979.)

<sup>39</sup> Hexamethonium has now been superseded by more modern hypotensive drugs. However, its value should not be underestimated, as it proved to be of major importance in the treatment of dangerously high blood pressure, at a time when few alternatives were available. See, M. Perutz, 'Health and the Medical Research Council', *Nature, Lond.*, 1972, 235: 191–192.

demonstration of their clinical potential,<sup>40</sup> led to increased interest in this field, and it was not surprising that, in 1949, the curariform action of suxamethonium was described by *three* independent groups in Italy, Great Britain, and the United States.

The Italian group, which first described the powerful neuromuscular blocking properties of suxamethonium, was led by Daniel Bovet (b. 1907).<sup>41</sup> They began work on synthetic curare substitutes in 1946, perhaps atypically, by studying molecules chemically similar to *d*-tubocurarine, going on to work with simpler compounds. In 1947, they described a new synthetic agent with a powerful competitive neuromuscular blocking action, which acquired the name Gallamine. The British group included James Walker (b. 1908), Gladwyn Albert Hurst Buttle (b. 1899), and Eleanor Zaimis. Walker was an organic chemist working at Hampstead; Buttle and Zaimis were pharmacologists. In fact, Zaimis had considerable chemical experience as well, with degrees in both chemistry and medicine. During the course of this work, she had synthesized many methonium compounds, some of them for the first time. The American group, based at the Wellcome Research Laboratories in New York State, comprised an organic chemist Arthur P. Phillips, and Julio C. Castillo (b. 1905) and Edwin J. de Beer (1902–1959),<sup>42</sup> who studied the pharmacology of suxamethonium. Both Paton<sup>43</sup> and Zaimis<sup>44</sup> believe that so much effort was put into the study of suxamethonium because of the success of decamethonium, a view confirmed by the original papers. The success of decamethonium was seen as a function of the distance between the two nitrogen atoms [i.e. ten carbon atoms]. Suxamethonium was considered a strong candidate because, as in decamethonium, the two nitrogen atoms were ten atoms apart (Fig. 2).

The other major reason for interest in suxamethonium was its similarity to two acetylcholine molecules laid end to end. In the British group, F. C. MacIntosh (also at Hampstead) pointed this out, and James Walker went on to make the compound. Additional evidence to support this view came from the American group; one of their publications explicitly called suxamethonium “diacetylcholine”.<sup>45</sup>

<sup>40</sup> The demonstration of the clinical potential of decamethonium was under way when the first reports on the synthesis and pharmacological properties of suxamethonium emerged. For an early demonstration of the clinical usefulness of decamethonium, see G. Organe, W. D. M. Paton and E. J. Zaimis, ‘Preliminary trials of bistrimethylammonium decane and pentane diiodide (C10 and C5) in man’, *Lancet*, 1949, i: 21.

<sup>41</sup> Bovet made many contributions to pharmacology, for which was awarded the Nobel Prize in 1957 (see Daniel Bovet, ‘The relationships between isomerism and competitive phenomena in the field of drug therapy of the autonomic nervous system and that of the neuromuscular transmission’, in *Nobel Lectures in Physiology or Medicine 1942–1962*, Amsterdam, Elsevier, 1964, pp. 552–578). He also synthesized antihistamines. Among the best accounts of Bovet’s work are: ‘Nobel laureates: Prof. Daniel Bovet’, *Nature, Lond.*, 1957, 180: 951; and Theodore L. Sourkes, *Nobel prize winners in medicine or physiology 1901–1965*, (revision of an earlier work by Lloyd G. Stevenson), London and New York, Abelard-Schuman, 1966, pp. 342–351.

<sup>42</sup> [Obituary], ‘Edwin John de Beer’, *New York Times*, 28 October 1959, p. 37.

<sup>43</sup> Paton, *op. cit.*, note 35 above.

<sup>44</sup> E. J. Zaimis, personal communication, 1978.

<sup>45</sup> J. C. Castillo and E. J. de Beer, ‘The neuromuscular blocking action of succinylcholine (diacetylcholine)’, *J. Pharmac. exp. Ther.*, 1950, 99: 458–464.

Barlow, in *op. cit.*, note 33 above, pointed out the structural similarity of two acetylcholine molecules with one molecule of decamethonium. Recently, F. C. MacIntosh claimed that the idea of “diacetylcholine” and its synthesis by Walker occurred at Hampstead some time before it was made and tested by



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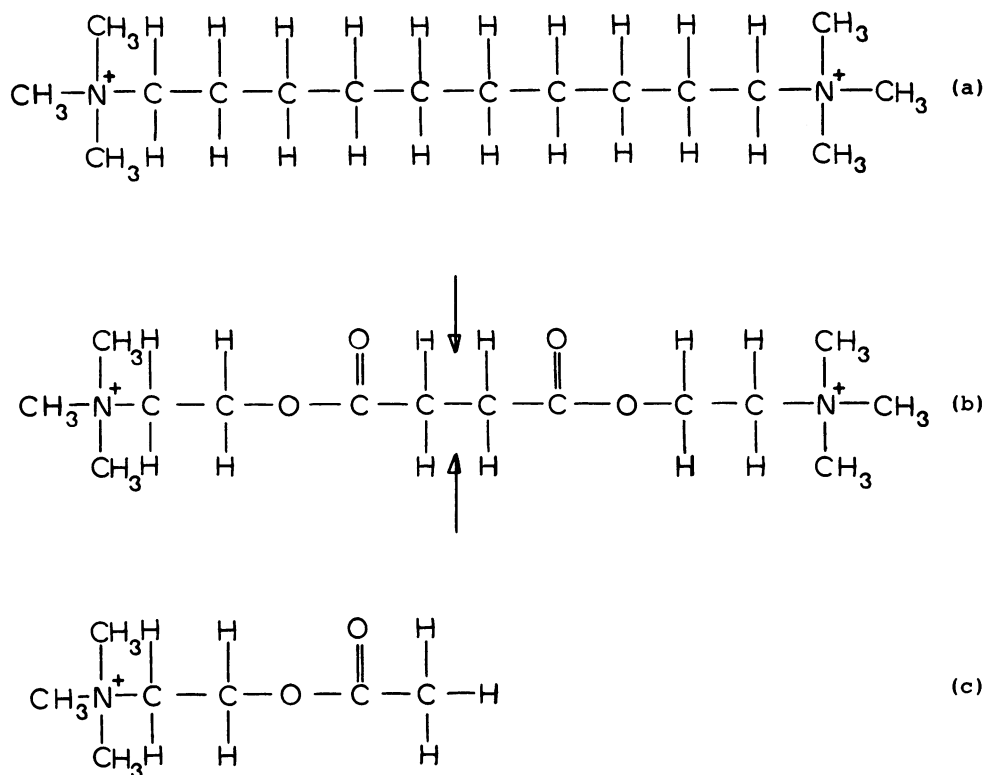


Figure 2.

(a) Decamethonium.

(b) Suxamethonium.

(c) Acetylcholine (ACh). This is the transmitter molecule at the neuromuscular junction in man. The fact that suxamethonium is diacetylcholine is shown on comparison of the chemical structure of ACh with that of suxamethonium (b). Suxamethonium is clearly two ACh molecules stuck end to end at the point shown by the arrows.

In 1949, the Italian group published their main paper on suxamethonium,<sup>46</sup> whilst in the same year, Buttle and Zaimis<sup>47</sup> and Phillips<sup>48</sup> presented papers on its phar-

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any other worker. He went on to state that he tested the drug, and that its very short duration of action led him to reject it. He did not realize that a short-acting drug has a number of practical advantages compared with a longer-acting blocking agent; for example, it facilitates the precise minute-to-minute control of the depth of neuromuscular block. This was confirmed by Walker. F. C. MacIntosh, 'The Sarrazin Lecture 1979: the age of bioassay, or my early stumbles on the trail of histamine and acetylcholine', *Canad. Physiol.*, 1979, 10: 65-79.

<sup>46</sup> D. Bovet, F. Bovet-Nitti, S. Guarino and V. G. Longo, 'Proprietà farmacodinamiche di alcuni derivati della succinilcolina dotati di azione curarica. Esteri di trialchiletanolammonio di acidi bicarbossilici alifatici', *Rc. Ist. sup. Sanita, Roma*, 1949, 12: 106-137.

<sup>47</sup> G. A. H. Buttle and E. J. Zaimis, 'The action of decamethonium iodide in birds', *J. Pharm. Pharmac.*, 1949, 1: 991-992.

<sup>48</sup> Arthur P. Phillips, 'Synthetic curare substitutes from aliphatic dicarboxylic acid aminoethyl esters', *J. Am. chem. Soc.*, 1949, 71: 3264. In the same year, the American group published their work on the

macology and synthetic chemistry respectively. The following year saw Walker's paper on suxamethonium synthesis,<sup>49</sup> and the pharmacological account of Castillo and de Beer.<sup>50</sup> Thus, several papers on the methonium compounds emerged quickly from a few laboratories around the world.

To what extent were these three groups truly independent? All three clearly knew of each other's work, both the American and the British workers specifically citing Bovet's work in their publications. The precise links are more difficult to ascertain. There were close contacts between Bovet and two British laboratories, the Pharmacology Department at Oxford<sup>51</sup> and the London School of Pharmacy (the home of Buttle and, briefly at this period, Zaimis).<sup>52,53</sup> However, there is nothing to suggest that the three reports on the chemical synthesis of suxamethonium are anything less than accounts of quite independent work.

#### 4. EARLIER WORK ON SUXAMETHONIUM

This account so far has portrayed the discovery of suxamethonium as a fairly logical process, starting with King's work on *d*-tubocurarine and moving through work on simple methonium compounds, culminating in the synthesis of suxamethonium itself. But, scientific research rarely progresses so tidily; there is more to the history of suxamethonium than is immediately evident. Bovet's synthesis of it was not the first; it is clear from his 1949 paper<sup>54</sup> that he knew of the work of Reid Hunt<sup>55</sup> and René de M. Taveau, two workers who prepared succinylcholine (suxamethonium) as early as 1906. In a paper published in that year, (i.e., fifteen years before Otto Loewi's classic experiments on chemical transmission and some thirty years before the demonstration of the role of acetylcholine in the neuromuscular junc-

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structurally similar decamethonium: J. C. Castillo, A. P. Phillips and E. J. de Beer, 'The curariform action of decamethylene - 1, 10 - bis-trimethylammonium bromide', *J. Pharmac. exp. Ther.*, 1949, 97: 150-156.

<sup>49</sup> J. Walker, 'Some new curarizing agents', *J. chem. Soc.*, 1950, 193-197.

<sup>50</sup> Castillo and de Beer, *op. cit.*, note 45 above.

<sup>51</sup> Bovet's group collaborated with the Oxford Pharmacology Department in the late 1940s. Edith Bülbring, a member of the Oxford department, went to Bovet's group for some months early in 1948, and this was followed by a visit to Oxford by Mlle. France Depierre from Bovet's laboratory at the Institut Pasteur, Paris. While in Oxford, Depierre worked with Bülbring on analogues of the competitive neuromuscular blocking agent Gallamine. This work was reported in: Edith Bülbring and France Depierre, 'The action of synthetic curarizing compounds on skeletal muscle and sympathetic ganglia both normal and denervated', *Br. J. Pharmac. Chemother.*, 1949, 4: 22-28. No work was done on succinylcholine during this visit. (E. Bülbring, personal communication, 1981.)

<sup>52</sup> G. A. H. Buttle was (and remains) a close friend of Bovet. In the 1930s, Buttle - then working at the Wellcome Laboratories - travelled to Paris every weekend to follow Bovet's progress. After World War II, Buttle was appointed to the Wellcome Chair of Pharmacology at the London School of Pharmacy, and continued to visit Bovet regularly while he was working on neuromuscular blocking agents. (G. A. H. Buttle, personal communication, 1981.) Autobiographical information may be found in: G. A. H. Buttle, 'A full circle', *Trends pharmacol. Sci.*, 1980, 1: 443-445.

<sup>53</sup> Professor Zaimis described the late forties as an intensely exciting time: a period of rapid advance in neuromuscular pharmacology. Zaimis, *op. cit.*, note 44 above.

<sup>54</sup> Bovet *et al.*, *op. cit.*, note 46 above.

<sup>55</sup> Reid Hunt (1870-1948) became chief of the Division of Pharmacology in the U.S. Public Health Service in 1906, and Professor of Pharmacology at Harvard from 1913 to 1926. See [Obituary], *New York Times*, 11 March 1948, p. 27; G. P. Grabfield, [obituary], *Science, N.Y.*, 1948, 108: 127.

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tion by Dale's group), they made telling comments. Writing of the physiological effects of choline and its derivatives, Hunt noted:

I have recently taken this subject up again in conjunction with Mr. Taveau and I desire today to report briefly some of our results. We have studied 19 such compounds, all but two of which, (the acetyl and benzoyl compounds) are new. *Acetyl-cholin*: Acetyl-cholin . . . is a substance of extraordinary physiological activity. In fact, I think it is safe to say that as regards its effect upon the circulation, it is the most powerful substance known. We have not determined the cause of the fall of blood pressure from acetyl-cholin, but from the fact that it can be prevented entirely by atropine, I am inclined to think that it is due to an effect upon the terminations of the vagus in the heart.<sup>56</sup>

Hunt, when describing his methods, mentioned that his results were obtained on thoroughly anaesthetized and curarized animals. Curare was used "so as to avoid any interference from effects upon the respiration". He then concluded: "Succinyl-cholin . . . was the only compound of the aliphatic dibasic acids studied, its physiological action is similar to that of the valeryl compound . . . causing a marked slowing of the heart". By curarizing his animals, Hunt had missed the neuromuscular blocking properties of suxamethonium. This then went undiscovered for over forty years. A further, and much more detailed report was published in 1911.<sup>57</sup> Here, Hunt and Taveau were concerned with the effects of choline and some eighty of its derivatives on the circulation and blood pressure, i.e., effects at autonomic ganglia and at a different type of receptor (muscarinic) site for acetylcholine, rather than with the effects at the nicotinic receptors of the neuromuscular junction. Succinylcholine was also mentioned in this report, but again no neuromuscular blocking action was described. One passage in this paper described an experiment to study the effects of acetylcholine on a non-curarized animal. On injecting acetylcholine, Hunt observed an atypical biphasic response in blood pressure. He also saw "slight muscular movements", and ascribed the cause of the changes in blood pressure to this muscle activity.<sup>58</sup>

What was the origin of Hunt's interest in choline and its derivatives? He had for some years been investigating the effects of extracts of the adrenal gland on blood pressure. It was well known that adrenalin raised the blood pressure, but Hunt had established that other extracts of the same gland could depress it. He had identified one of these as choline, but had also shown that this was not the only hypotensive constituent of these extracts. This caused him to begin the systematic study of choline and its derivatives, during which he synthesized suxamethonium.

However, the work of Hunt and Taveau did not represent the last appearance of succinylcholine before 1949. Some ten years after the publication of their second paper, Le Heux in Germany worked on the effect of succinylcholine on *in vitro* rabbit

<sup>56</sup> Reid Hunt and R. de M. Taveau, 'On the physiological action of certain cholin derivatives and new methods for detecting cholin', *Br. med. J.*, 1906, ii: 1788–1791.

<sup>57</sup> *Idem*, 'The effects of a number of derivatives of choline and analogous compounds on the blood-pressure', *Bull. hyg. Lab., Wash.*, 1911, 73.

<sup>58</sup> Sadly, Hunt did not continue to study acetylcholine, nor did he realize that movement of the muscle was caused by acetylcholine acting directly on it. Hunt and Taveau were not the only workers before Dale's group to deal with the action of acetylcholine on muscle; an example is the work of Otto Riesser, 'Beitrag zur Kenntnis des Acetylcholins', *Arch. exp. Path. Pharmacol.*, 1931, 161: 34.

An excellent guide to the literature of the early period of transmitter work is: J. H. Gaddum, *Gefasserweiternde Stoffe der Gewebe*, Leipzig, Thieme, 1936. Translated by W. Feldberg, it appeared only in German. (H. Blaschko, personal communication, 1979.)

intestine, in connexion with studies on choline and its derivatives. He reported it to have only a relatively slight effect on peristalsis.<sup>59,60</sup> In 1941, Glick synthesized suxamethonium (for what he thought was the first time) and showed its susceptibility to hydrolysis.<sup>61</sup>

Thus it is clear that the synthesis and description of the pharmacological actions of suxamethonium had been a series of "near misses" until Bovet finally observed neuromuscular block in 1949. Why did Bovet find an effect that had eluded three other groups? Part of the answer is that he was the first to produce experimental conditions conducive to the appearance of neuromuscular blocking action, e.g., the use of animals not given curare which would mask this action. It is tempting to suggest that Bovet was the first to succeed because, unlike his predecessors, he knew what he was looking for. Experience with decamethonium had shown neuromuscular blocking action to be associated with a polymethylene *bis*trimethylammonium structure (the structure of the methonium series), and it now seems natural enough to move from the ten carbon atom separation of the two nitrogen atoms in decamethonium to the same separation in suxamethonium. One other factor contributed to Bovet's success: the fact that he worked many years after Dale, when the transmitter role of acetylcholine was well established.

Some twenty years after Bovet's paper, the theoretical basis of the synthesis of the methonium compounds was to be questioned. As mentioned above, the starting-point for Bovet's work was the elucidation of the structure of *d*-tubocurarine by King in 1935. The structure was subsequently revised in 1939<sup>62</sup> and 1948.<sup>63</sup> These revisions were not important in terms of their implications for the development of suxamethonium, in that no structural modifications were suggested at either of the two nitrogen atoms. Barlow and Ing synthesized the methonium compounds with the double quaternary configuration of *d*-tubocurarine in mind. Ironically, in 1970, Everett *et al.*<sup>64</sup> reported that *d*-tubocurarine does not contain two quaternary nitrogen atoms (Fig. 1c).<sup>65,66</sup>

<sup>59</sup> S. Thesleff, 'Succinylcholine Iodide - studies on its pharmacological properties and clinical use', *Acta physiol. scand.*, 1952, **27**, Suppl. 99.

<sup>60</sup> J. W. Le Heux, 'Cholin als Hormon der Darmbewegung. III Mitteilung: Die Beteiligung des Cholins an der Wirkung verschiedener organischer Säuren auf den Darm', *Pflügers Arch. Ges. Physiol.*, 1921, **190**: 280-300.

<sup>61</sup> David Glick, 'Some additional observations on the specificity of cholinesterase', *J. biol. Chem.*, 1941, **137**: 357-362.

<sup>62</sup> Harold King, 'Curare alkaloids. Part IV - bebeerine and tubocurarine, orientation of phenolic groups', *J. chem. Soc.*, 1939, 1157-1164.

<sup>63</sup> *Idem*, 'Curare alkaloids. Part VII - constitution of *dextro*-tubocurarine chloride', *ibid.*, 1948, 265-266.

<sup>64</sup> A. J. Everett, L. A. Lowe and S. Wilkinson, 'Revision of the structures of (+) - tubocurarine chloride and (+) - chondrocurine', *Chem. Commun.*, 1970, 1020-1021.

<sup>65</sup> The revised structure was confirmed in 1973, in a thorough crystallographic analysis: P. W. Codding and M. N. G. James, 'The crystal and molecular structure of a potent neuromuscular blocking agent: *d*-tubocurarine dichloride pentahydrate', *Acta Crystallogr.*, 1973, **29B**: 935-942.

<sup>66</sup> The reason for the error in King's structure for *d*-tubocurarine is well explained by MacLagan. In much of his chemical work, King used the dimethyl ether of *d*-tubocurarine. There is now little doubt that the chemical reaction that yields the dimethyl ether also causes the replacement of a hydrogen atom at one nitrogen atom by a methyl group, i.e., the dimethyl ether is a diquaternary nitrogen compound. (Jennifer MacLagan, 'Competitive neuromuscular blocking drugs', in Eleanor Zaimis (editor), *Handbook of experimental pharmacology*, vol. 42: *Neuromuscular junction*, Berlin, Heidelberg, and New York, Springer, 1976, pp. 421-486.)

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A group of very useful drugs was thus discovered on the premise that *d*-tubocurarine was a diquaternary salt, an assumption later found to be inaccurate.<sup>67</sup>

### 5. CLINICAL APPLICATION

Following the synthesis of suxamethonium in the late 1940s, the drug was clinically tested in the early 1950s. The areas in which it would be useful were to some extent already known, because of the earlier careful evaluation of decamethonium (1949–1953). Suxamethonium, a neuromuscular blocking agent, would be useful in producing a profound muscle relaxation. As Dripps<sup>68</sup> points out, “Muscle relaxation of varying degrees is needed in many surgical procedures . . . relaxation of the jaw muscles assists intubation of the trachea, and the reduction of a dislocated shoulder can be facilitated by the use of a muscle relaxant”. Muscle relaxation is also very helpful in abdominal surgery. The other important application of suxamethonium was also easily predicted: as a short-acting curare substitute to protect patients undergoing ECT.

Paton<sup>69</sup> identifies two figures with key roles in advancing the use of suxamethonium: in America, an anaesthesiologist, Francis Foldes; and in Sweden, Stephen Thesleff. Feldman<sup>70</sup> notes the contributions of Brucke and his associates and Mayrhofer and Hassfurth in Austria;<sup>71</sup> and Scurr<sup>72</sup> and Bourne and his colleagues in the U.K., in introducing suxamethonium in their countries.

<sup>67</sup> The structure-activity relation of the *d*-tubocurarine molecule has remained a topic for detailed scrutiny. It has been pointed out that although the molecule is not diquaternary, it is likely to have two positively charged centres at normal physiological pH, because the tertiary nitrogen atom will be protonated. See W. C. Bowman and M. J. Rand, *Textbook of pharmacology*, 2nd ed., Oxford, Blackwell Scientific, 1980, ch. 17, p. 34.

The notion of the existence of an optimal distance of separation of the two nitrogen atoms for neuromuscular blocking activity has now been called into question. This idea was important as the basis of the work of Ing and others. However, it has been pointed out that while the distance between the two quaternary ammonium groups in *d*-tubocurarine is 1.4–1.5 nm, pancuronium, a competitive blocking agent four to five times more potent, has a separation of 1.0–1.1 nm, while the new blocking drug fazadinium (also called AH 8165) has 0.7 nm between its two quaternary ammonium groups. Furthermore, the role of the quaternary ammonium groups is not clear, the neuromuscular blocking activity of  $\beta$ -erythroidine and dihydro- $\beta$ -erythroidine is abolished when the tertiary nitrogen atoms are made quaternary. See: S. A. Feldman, ‘Neuromuscular blocking drugs’, in H. C. Churchill-Davidson (editor), *A practice of anaesthesia*, 4th ed., London, Lloyd-Luke, 1978, p. 865; Palmer Taylor, ‘Neuromuscular blocking agents’, in Alfred Goodman Gilman *et al.*, (editors), *The pharmacological basis of therapeutics*, 6th ed., New York, Macmillan, 1980, pp. 220–234.

Finally, it would appear that *d*-tubocurarine does not have a purely competitive mode of action. A very thorough recent analysis suggests that under some circumstances, *d*-tubocurarine blocks the flow of ions that causes the depolarization of the muscle end plate, rather than simply competing with acetylcholine for receptor sites. See D. Colquhoun, ‘Competitive block and ion channel block as mechanisms of antagonist action in the skeletal muscle end-plate’, in G. Pepeu *et al.* (editors), *Receptors for neurotransmitters and peptide hormones*. (*Advances in biochemical psychopharmacology*, vol. 21), New York, Raven Press, 1980, pp. 67–80.

<sup>68</sup> Robert D. Dripps, ‘The clinician looks at neuromuscular blocking drugs’, in Zaimis, *op. cit.*, note 66 above, pp. 583–592.

<sup>69</sup> Paton, *op. cit.*, note 35 above.

<sup>70</sup> Feldman, *op. cit.*, note 67 above.

<sup>71</sup> O. Mayrhofer and M. Hassfurth, ‘Kurzwirkende Muskelerlähfungsmittel; Selbstversuche und klinische Erprobung am narkotisierten Menschen’, *Wien. klin. Wschr.*, 1951, **63**: 885–889.

<sup>72</sup> C. F. Scurr, ‘A relaxant of very brief action’, *Br. med. J.*, 1951, **ii**: 831–832.

The years 1950–53 witnessed intense activity; the drug was selectively tried out on a few patients, generally found to be successful, and papers by practising clinicians in clinical journals around the world brought it to the attention of their colleagues.<sup>73 74 75</sup> Many of these papers referred to suxamethonium by its other name, succinylcholine. The latter name more accurately reflects its composition as an ester of two choline moieties with the dicarboxylic acid, succinic acid. It was known before the start of clinical trials that suxamethonium was a short-acting drug. In 1941, Glick<sup>76</sup> discovered that it was very rapidly hydrolysed by non-specific “esterase” enzymes found in the blood plasma.<sup>77</sup> This was subsequently confirmed by Bovet-Nitti in 1949.<sup>78</sup> Ten years later, it was shown that the product of succinylcholine hydrolysis was succinylmonocholine.<sup>79</sup> This is an intermediate, which is subsequently hydrolysed to succinate and choline. Succinylmonocholine was considered by Bovet to be pharmacologically inactive<sup>80</sup> but was later shown to have blocking properties similar to those of suxamethonium but with much lower potency.<sup>81</sup> Choline also has some neuromuscular blocking activity, but at physiological concentrations this is unlikely to have a significant effect. Paton<sup>82</sup> considers suxamethonium’s susceptibility to hydrolysis to be important in its development as a drug, yet he also points out that brevity of action is one possible explanation why suxamethonium did not replace decamethonium as the muscle relaxant of choice earlier, for at that time the “target” neuromuscular blocking agent was a long-acting drug.

The initial clinical trials went very well,<sup>83,84,85,86</sup> and in March 1952, von Dardel and Thesleff wrote: “Muscular relaxation was found to be satisfactory in every case. No cumulative effect or tachyphylaxis was observed. No complications or toxic actions were encountered, either during anaesthesia or post-operatively, that could be

<sup>73</sup> H. Brucke, K. H. Ginzel, H. Klupp, F. Pfaffenschlager and G. Werner, ‘Bischolinester von Dicarbonsauren als Muskelrelaxanter in der Narkose’, *Wien. klin. Wschr.*, 1951, 63: 464–466.

<sup>74</sup> S. Thesleff, ‘Pharmacological and clinical tests with L.T.1 (0.0-succinylcholine iodide)’, *Nord. Med.*, 1951, 46: 1045.

<sup>75</sup> O. von Dardel and S. Thesleff, ‘Clinical results with succinylcholine iodide, a new muscle relaxant’, *ibid.*, 1951, 46: 1308–1311.

<sup>76</sup> It is clear that Glick’s main interest was in the enzymes responsible for the hydrolysis of choline esters. Although he synthesized suxamethonium, this was only used as a “biochemical probe” to study the cholinesterases.

<sup>77</sup> Glick, *op. cit.*, note 61 above.

<sup>78</sup> F. Bovet-Nitti, ‘Degradazione di alcune sostanze curanzanti per azione di colinesterasi’, *Re. Ist. sup. Sanita. Roma*, 1949, 12: 138–157.

<sup>79</sup> V. P. Whittaker and S. Wijesundera, ‘The hydrolysis of succinylcholine by cholinesterase’, *Biochem. J.*, 1952, 52: 475–479.

<sup>80</sup> D. Bovet, F. Bovet-Nitti, S. Guarino, V. G. Longo and R. Fusco, ‘Recherches sur les poisons curarizants de synthèse; succinylcholine et dérivés aliphatiques’, *Archs. int. Pharmacodyn. Ther.*, 1951, 88: 1–50.

<sup>81</sup> H. Lehmann and E. Silk, ‘Succinylmonocholine’, *Br. med. J.*, 1953, i: 767–768.

<sup>82</sup> Paton, *op. cit.*, note 35 above. See also note 45 above.

<sup>83</sup> Brucke, *op. cit.*, note 73 above.

<sup>84</sup> Von Dardel and Thesleff, *op. cit.*, note 75 above.

<sup>85</sup> O. von Dardel and S. Thesleff, Communication to the twenty-sixth International Congress on Anaesthesiology, London, September 1951.

<sup>86</sup> G. Holmberg and S. Thesleff, ‘Succinylcholine as a muscle relaxant in electroshock therapy’, *Nord. Med.*, 1951, 46: 1567–1569.

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ascribed to the use of succinylcholine iodide as a muscular relaxant".<sup>87</sup> Similarly, in June 1952, Foldes noted: "Its use is not accompanied by unwanted side effects and the incidence of post-operative complications after its use is low. On the basis of limited experience, succinylcholine seems to be the muscle relaxant of choice of all similar agents so far investigated."<sup>88</sup>

### 6. SUXAMETHONIUM AND THE DEVELOPMENT OF PHARMACOGENETICS

Suxamethonium would have been exceptional indeed if it had had no major side-effects. When individual sensitivity to a drug varies by a factor of at least three, this is not surprising. Before publication, Foldes included an addendum to his paper of June 1952, drawing attention to reports of several instances of respiratory depression following the use of suxamethonium. These reports<sup>89,90,91,92</sup> were the first indications of its associated side-effects,<sup>93</sup> which, typically, came to light only after the start of relatively large-scale trials. These reports were atypical in marking the start of a new phase in the history of suxamethonium: its contribution to the then very young and developing science of pharmacogenetics.

The term "pharmacogenetics" – the study of the genetic component in the response of an individual to a drug – was not coined until 1957.<sup>94</sup> The contribution of suxamethonium to the development of pharmacogenetics illustrates how, in the attempts to unravel a problem, the nature of the scientific questions asked inevitably limits the usefulness of the answers in its solution.

Probably the best early review of the difficulties with the clinical application of suxamethonium is that by Bourne *et al.*<sup>95</sup> This paper, and one by Evans *et al.*<sup>96</sup> in the same issue of the *Lancet*, put into perspective the problems of prolonged apnoea.

<sup>87</sup> O. von Dardel and S. Thesleff, 'Succinylcholine iodide as a muscle relaxant', *Acta Chir. Scand.*, 1952, 103: 321–336.

<sup>88</sup> F. Foldes, P. G. McNall and J. M. Borrego-Hinojosa, 'Succinylcholine: A new approach to muscular relaxation in anesthesiology', *Proc. Can. Anaesth. Soc.*, 1952, 38.

<sup>89</sup> S. H. S. Love, 'Prolonged apnoea following scoline', *Anaesthesia*, 1952, 7: 113–114.

<sup>90</sup> R. B. Gould, 'Succinylcholine chloride', [Correspondence], *Br. med. J.*, 1952, i: 440.

<sup>91</sup> J. K. Harper, 'Prolonged respiratory paralysis after succinylcholine', [Correspondence], *ibid.*, 866.

<sup>92</sup> C. L. Hewer, *ibid.*, 971–972.

<sup>93</sup> Whilst these reports were the first to be published, Lehmann received a communication from Davies in 1951 describing an apparently healthy soldier who had virtually no plasma pseudocholinesterase. H. Lehmann, E. Silk and J. Liddell, 'Pseudo-cholinesterase', *Br. med. Bull.*, 1961, 17: 230–233.

<sup>94</sup> It is difficult to overestimate the importance of suxamethonium in the development of pharmacogenetics. The response to this drug was one of the two drug reactions based on genetically controlled enzyme aberrations that provided the starting-point for studies in this area. (The other drug response was the sensitivity of some individuals to the anti-malarial drug primaquine, shown to be the result of abnormalities in red cell glutathione metabolism.) See: A. G. Motulsky, 'Pharmacogenetics and ecogenetics: the problem and its scope', in F. Vogel *et al.* (editors), *Human genetic variation in response to medical and environmental agents: pharmacogenetics and ecogenetics*, (*Human Genetics*, supplement 1), Berlin, Heidelberg, and New York, Springer, 1978, pp. 1–3; *idem*, 'Drug reactions, enzymes and biochemical genetics', *J. Am. med. Ass.*, 1957, 165: 835–837; F. Vogel, 'Moderne Probleme der Humangenetik', *Ergebn. inn. Med. Kinderheilk.*, 1959, 12: 52; A. G. Motulsky, 'History and current status of pharmacogenetics', in *Human genetics. Proc. 4th Internat. Congr. hum. Genet. (Paris, 1971)*, Amsterdam, Excerpta Medica, 1972, pp. 381–390.

<sup>95</sup> J. G. Bourne, H. O. J. Collier and G. F. Somers, 'Succinylcholine – muscle relaxant of short action', *Lancet*, 1952, i: 1225–1229.

These papers also contained the first clues as to the mechanism of this phenomenon. The enzymatic hydrolysis of suxamethonium had been known for some eleven years, so it was thought that the plasma cholinesterase levels of suxamethonium-sensitive patients should be compared with those of normal patients. It was found that "those patients who recovered unusually slowly from succinylcholine had significantly lower plasma-cholinesterase levels than did patients who recovered at the normal speed".<sup>96a</sup> Significantly, the test used to measure the activity of plasma-cholinesterase involved the evolution of carbon dioxide from a bicarbonate buffer by the products of ester hydrolysis. It was assumed that the test accurately reflected the level of plasma-cholinesterase present in the patient. It was known that certain conditions, such as insecticide poisoning, malnutrition, and liver disease could depress levels of the enzyme.<sup>97</sup> At the time, this mechanism was not the only explanation put forward. Acidaemia, synergism of suxamethonium with thiopentone, hyperventilation, and overdosage of the drug were all suggested.<sup>98</sup> There are many possible causes of apnoea, however, although the evidence favouring the enzyme as the major determining factor was by far the most persuasive. Evans *et al.* concluded their paper with the advice: "not to give succinylcholine to patients likely to have a low serum esterase level, such as may be found in liver disease, severe anaemia and after poisoning with anti-cholinesterase compounds".<sup>99</sup> The problem seemed solved, but then several cases were reported where none of the above factors applied: "the patients appear to be in good health, yet they show prolonged reaction to succinylcholine and a correspondingly low pseudocholinesterase level".<sup>100,101,102</sup> In 1953, Forbat *et al.* came across one such case and decided to investigate the patient's relatives.<sup>103</sup> They found that his brother also had a low serum esterase level; and since he, too, was in all other respects healthy, this pointed to a genetic factor in the aetiology of suxamethonium sensitivity. Some three years later, one of the authors of the 1953 paper, Lehmann, published with Ryan a study of the families of five unrelated suxamethonium-sensitive individuals and suggested that the evidence pointed to "a recessive gene being responsible".<sup>104</sup>

The next important contribution in unravelling this problem came from Kalow, a

<sup>96</sup> F. T. Evans, P. S. W. Gray, H. Lehmann and E. Silk, 'Sensitivity to succinylcholine in relation to serum cholinesterase', *ibid.*, 1229-1230.

<sup>96a</sup> Bourne *et al.*, *op. cit.*, note 95 above, p. 1227.

<sup>97</sup> It is interesting to note that Evans and his co-workers only became interested in suxamethonium through plasma cholinesterase. Their work arose from a study of the use of plasma cholinesterase as a guide to the functioning of the liver. (See note 79 above.)

<sup>98</sup> A. Forbat, H. Lehmann and E. Silk, 'Prolonged apnoea following injection of succinylcholine', *Lancet*, 1953, ii: 1067-1068.

<sup>99</sup> Evans *et al.*, *op. cit.*, note 96 above.

<sup>100</sup> Forbat *et al.*, *op. cit.*, note 98 above.

<sup>101</sup> J. G. Bourne, 'Long action of suxamethonium (succinylcholine) chloride', *Br. J. Anaesth.*, 1953, 25: 116-129.

<sup>102</sup> See also note 93 above.

<sup>103</sup> *Op. cit.*, note 98 above. This step was to prove critical in the solution of the problem. Lehmann, in retrospect, considers that interest in the various "haemoglobinopathies", which also have a genetic component, was the reason why this group took this step.

<sup>104</sup> H. Lehmann and E. Ryan, 'The familial incidence of low pseudocholinesterase level', *Lancet*, 1956, ii: 124.



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pharmacologist who was to contribute much to the field of pharmacogenetics. In a succession of papers in the late fifties, he and his co-workers demonstrated that the presence of an abnormal enzyme rather than a lack of normal serum-cholinesterase made certain otherwise healthy individuals sensitive to suxamethonium.<sup>105,106,107,108</sup> This conclusion differs from those made on the basis of earlier work. Because the atypical form of the enzyme has less affinity for a substrate, e.g. suxamethonium, the early observations had suggested less cholinesterase physically present in drug-sensitive patients. In otherwise healthy patients, this was simply not the case – the tests used were at fault because they reflected cholinesterase *activity*, rather than the *amount* of enzyme, yet they were interpreted in terms of the latter.<sup>109,110,111</sup> Such abnormal enzymes had kinetic properties markedly different from normal – suxamethonium and other substrates having a much lower avidity for the abnormal enzyme. At typical concentrations of suxamethonium present during anaesthesia, the abnormal enzyme has no detectable effect on the drug in contrast to the marked hydrolytic effect of normal enzyme.<sup>112</sup> Using a variety of methods, it has since been shown that at least one of the two sites on the plasma-cholinesterase molecule which normally bind a choline ester molecule is altered.<sup>113</sup> Further work has suggested that the “esteratic” site as well as the “anionic” site may be altered.<sup>114,115</sup>

The problem was made clearer by Kalow and his co-workers. A local anaesthetic called Dibucaine (Nupercaine, Cinchocaine) was found to inhibit normal and atypical forms of serum cholinesterase differentially. The gene responsible for the atypical cholinesterase molecule is now designated  $E_1^a$ , while the normal form is shown as  $E_1^u$ . Using this inhibitor, three distinct groups were characterized: (i) Individuals with an enzyme that could be 80% inhibited. These were normal individuals carrying two genes for the normal enzyme – homozygotes [ $E_1^u E_1^u$ ]. (ii) Suxamethonium-sensitive individuals homozygous for the abnormal enzyme, which was 20% inhibited by Dibucaine [ $E_1^a E_1^a$ ] (iii) Heterozygous individuals who carry one gene for normal enzyme, and one for atypical enzyme. This group, which produced a mixture of enzymes was intermediate, showing 52–69% inhibition. The syndrome of suxamethonium sensitivity was thus clearly shown to have a genetic basis.

<sup>105</sup> W. Kalow and K. Genest, ‘A method for the detection of atypical forms of human serum cholinesterase. Determination of dibucaine numbers’, *Can. J. Biochem. Physiol.*, 1957, **35**: 339–346.

<sup>106</sup> W. Kalow and N. Staron, ‘On the distribution and inheritance of atypical forms of human serum cholinesterase as indicated by Dibucaine numbers’, *ibid.*, 1957, **35**: 1305–1320.

<sup>107</sup> R. O. Davies, A. V. Marton and W. Kalow, ‘The action of normal and atypical cholinesterase of human serum upon a series of esters’, *ibid.*, 1960, **38**: 545–551.

<sup>108</sup> W. Kalow and R. O. Davies, ‘The activity of various esterase inhibitors towards atypical human serum cholinesterases’, *Biochem. Pharmacol.*, 1959, **1**: 183–192.

<sup>109</sup> Evans *et al.*, *op. cit.*, note 96 above.

<sup>110</sup> Forbat *et al.*, *op. cit.*, note 98 above.

<sup>111</sup> H. Lehmann and P. H. Simmons, ‘Sensitivity to suxamethonium apnoea in two brothers’, *Lancet*, 1958, **ii**: 981–982.

<sup>112</sup> Davies *et al.*, *op. cit.*, note 107 above.

<sup>113</sup> Kalow and Davies, *op. cit.*, note 108 above.

<sup>114</sup> S. W. Clark, G. A. Glaubiger and B. N. La Du, ‘Properties of plasma cholinesterase variants’, *Ann. N. Y. Acad. Sci.*, 1968, **151**: 710–722.

<sup>115</sup> E. S. Vesell, ‘Recent progress in pharmacogenetics’, *Adv. Pharm. Chemother.*, 1969, **7**: 1–52.

Kalow's work showed that inheritance of the atypical enzyme was in a genetic system where two non-dominant alleles – "normal" and "atypical" – operated [ $E_1$ ,  $E_1^a$ ]. It is important to note that the substrate used in the Dibucaine experiments of Kalow and co-workers was benzoylcholine, not suxamethonium, because it was much easier technically to follow the former's hydrolysis reaction. Benzoylcholine could be used because it too is a choline ester. Benzoic acid is, however, a monobasic carboxylic acid. This study, therefore, was based on the assumption that the hydrolysis of benzoylcholine by plasmacholinesterase was a good kinetic and mechanistic model for the breakdown of suxamethonium.<sup>116</sup> The use of an inhibitor in the study of atypical enzyme molecules was important, and, not surprisingly, this idea was subsequently used by other workers. In the early 1960s, the inhibitor method was again applied, using fluoride instead of dibucaine. Another allele on the same gene locus was discovered, producing an enzyme which could hydrolyse suxamethonium at an intermediate rate.<sup>117,118</sup> This has been designated  $E_1^f$ . A number of other inhibitors have been used. These include urea,<sup>119,120</sup> sodium chloride,<sup>121</sup> n-butanol,<sup>122</sup> and suxamethonium itself.<sup>123</sup> All of these have been used in systems using benzoylcholine as substrate. Some of these inhibitors, notably sodium chloride<sup>124</sup> and n-butanol, have been shown to inhibit some samples of plasmacholinesterase in unusual ways and have resulted in the postulation of other alleles at this locus, which are not shown up well in conventional Dibucaine tests.

More rarely, individuals who lack functional enzyme have been found.<sup>125,126</sup> Such individuals are very susceptible to suxamethonium, and have to be ventilated for several hours until the drug (which is not broken down enzymatically) is excreted.<sup>127</sup>

<sup>116</sup> A simple spectrophotometric method for following the hydrolysis of benzoylcholine, based on measurement of absorbance at  $240\mu$  was developed early on. See W. Kalow and H. A. Lindsay, 'A comparison of optical and manometric methods for the assay of human serum cholinesterase', *Can. J. Biochem. Physiol.*, 1955, 33: 568–574.

A brief description of the problems with methods based on the hydrolysis of succinylcholine used before 1975 can be found in H. W. Goedde and D. P. Agarwal, 'Pseudocholinesterase Variation', in Vogel *et al.*, op. cit., note 94 above, pp. 45–55.

<sup>117</sup> H. Harris and M. Whittaker, 'Differential inhibition of human serum cholinesterase with fluoride: recognition of two new phenotypes', *Nature, Lond.*, 1961, 191: 496–498.

<sup>118</sup> *Idem*, 'The serum cholinesterase variants. A study of 22 families selected via the "intermediate" phenotype', *Ann. hum. Genet.*, 1962, 26: 59–72.

<sup>119</sup> H. K. Hanel and J. Vilby Mogensen, 'Urea inhibition of human pseudocholinesterase', *Br. J. Anaesth.*, 1971, 43: 51–53.

<sup>120</sup> *Idem*, 'The inhibition of serum cholinesterase by urea', *ibid.*, 1977, 49: 1251–1257.

<sup>121</sup> M. Whittaker, 'The pseudocholinesterase variants. Differentiation by means of sodium chloride', *Acta. genet. statist. med.*, 1968, 18: 556–562.

<sup>122</sup> *Idem*, 'Differential inhibition of human serum cholinesterase with n-butylalcohol: recognition of new phenotypes', *ibid.*, 335–340.

<sup>123</sup> J. King and D. Griffin, 'Differentiation of serum cholinesterase variants by succinylcholine inhibition', *Br. J. Anaesth.*, 1973, 45: 450–454.

<sup>124</sup> M. Whittaker, 'An additional pseudocholinesterase phenotype occurring in suxamethonium apnoea', *ibid.*, 1968, 40: 579–582.

<sup>125</sup> J. Liddell, H. Lehmann and E. Silk, 'A "silent" pseudocholinesterase gene', *Nature, Lond.*, 1962, 193: 561–562.

<sup>126</sup> S. M. Hart and J. V. Mitchell, 'Suxamethonium in the absence of pseudocholinesterase', *Br. J. Anaesth.*, 1962, 34: 207–209.

<sup>127</sup> S. E. Smith, 'Neuromuscular blocking drugs in man', in Zaimis, op. cit., note 66 above, pp. 593–660.

Such individuals have what pharmacogeneticists call "silent" genes; homozygotes occurring at the rate of 1 per 100,000 people. A survey of the literature on the silent gene revealed that the majority of the world population described as having the silent gene are Eskimos – partly due to inbreeding in an isolated Alaskan Eskimo population.<sup>128</sup> The silent gene (designated  $E_1^A$ ) has subsequently been shown to be heterogeneous. It was initially unclear whether it was the gene or its product, the enzyme, that was "silent". It has since been shown that both these alternatives can be found in nature: some individuals carrying the silent gene have very low enzyme activity, about 2–8% of the normal level of cholinesterase activity, while there is another group with no enzyme activity at all.<sup>129–133</sup> It is thought that individuals bearing the silent gene specifying the latter type of defect simply produce no enzyme at all. The allele resulting in absence of enzyme is now designated  $E_1^S$ , while the allele characterized by low enzyme activity is designated  $E_1^T$ . A third variant within the silent group,  $E_1^R$ , also with less than 10% of the normal activity was recently found in an Alaskan Eskimo.<sup>134</sup> Other silent gene variants may yet be discovered.

Individuals with abnormally high cholinesterase activity have also been reported. There are two types. One, present in the British population, results in an average level of serum cholinesterase activity some 30% above normal, a margin too slight to have clinical significance.<sup>135</sup> Individuals with this variant possess an extra serum cholinesterase component, designated  $C_s$ . The second version, discovered in Cynthiana, Kentucky,<sup>136</sup> and therefore now designated  $E_{Cynthiana}$ <sup>137</sup> confers resistance to suxamethonium. Individuals with this allele were shown to hydrolyse the drug much faster – the plasma enzyme activity being three times the normal. This variant has both a qualitative and a quantitative dimension: a biochemically different cholinesterase molecule is being produced, as in the examples described above, but also there is an elevated amount of enzyme present in the serum of individuals with this allele.

<sup>128</sup> B. B. Gutsche, E. M. Scott and R. C. Wright, 'Hereditary deficiency of pseudocholinesterase in Eskimos', *Nature, Lond.*, 1967, **215**: 322–323.

<sup>129</sup> H. W. Goedde, D. Gehring and R. Hoffman, 'On the problem of a "silent gene" in the polymorphism of pseudocholinesterases', *Biochim. Biophys. Acta*, 1965, **107**: 391–393.

<sup>130</sup> H. W. Goedde and K. Altland, 'Suxamethonium sensitivity', *Ann. N.Y. Acad. Sci.*, 1971, **179**: 695–703.

<sup>131</sup> W. E. Hodgkin, E. R. Giblett, H. Levine, W. Bauer and A. G. Motulsky, 'Complete pseudocholinesterase deficiency: genetic and immunologic characterization', *J. clin. Inv.*, 1965, **44**: 486–493.

<sup>132</sup> E. M. Scott, 'Inheritance of two types of deficiency of human serum cholinesterase', *Ann. hum. Genet.*, 1973, **37**: 139–143. See also, Gutsche, op. cit., note 128 above.

<sup>133</sup> H. W. Goedde and K. Altland, 'Evidence for the different "silent genes" in the human serum pseudocholinesterase polymorphism', *Ann. N.Y. Acad. Sci.*, 1968, **151**: 540–544.

<sup>134</sup> E. M. Scott and R. C. Wright, 'A third type of serum cholinesterase deficiency in Eskimos', *Am. J. hum. Genet.*, 1976, **28**: 253–256.

<sup>135</sup> H. Harris, D. A. Hopkinson, E. B. Robson and M. Whittaker, 'Genetical Studies on a new variant of serum cholinesterase detected by electrophoresis', *Ann. hum. Genet.*, 1963, **26**: 359–382.

<sup>136</sup> H. W. Neitlich, 'Increased plasma cholinesterase activity and succinylcholine resistance: a genetic variant', *J. clin. Invest.*, 1966, **45**: 380–387.

<sup>137</sup> A. Yoshida and A. G. Motulsky, 'A pseudocholinesterase variant ( $E_{Cynthiana}$ ) associated with elevated plasma enzyme activity', *Am. J. hum. Genet.*, 1969, **21**: 486–498.

The concept of quantitative variation in plasmacholinesterase levels has only recently been considered to have a genetic basis. This is probably for two reasons: first, the idea that abnormal response to suxamethonium was solely a function of the *amount* (cf. the *activity*) of plasmacholinesterase was, as we have seen, an idea which confused much of the early thinking about this problem. Second, a number of well-documented causes of reduced enzyme levels (e.g., liver disease) exist.<sup>138</sup> It is clearly difficult to distinguish between these conditions where the synthesis of normal enzyme is depressed because of disease or malnutrition, and genetic determinants causing reduced synthesis of normal enzyme. Nonetheless, two quantitative variants have recently been described. One of these,  $E_1^j$ , causes a 65–70% reduction in circulating normal cholinesterase molecules,<sup>139,140</sup> while the other,  $E_1^k$ , causes a 33% reduction.<sup>141,142</sup>

As we have noted, the substrate used in nearly all of the studies described above was benzoylcholine, not suxamethonium. This further illustrates that the way in which the problem was approached has necessarily limited the usefulness of the answers. The use of benzoylcholine in tests on sera from affected patients provided no information on the ability of these sera to hydrolyse suxamethonium. It is clearly desirable to use suxamethonium itself as a substrate in these assays. This innovation really had to await the development in 1975 of a convenient method for following the hydrolysis reaction,<sup>143,144</sup> whereby samples of sera previously classified as normal, which came from patients with a history of prolonged apnoea, were reexamined with suxamethonium as substrate and Dibucaine as inhibitor. This has resulted in the discovery of a new variant with altered properties toward succinylcholine but not toward benzoylcholine. The new variant has been provisionally designated  $E_1^{su}$ , although further investigation is necessary. This technique may reveal several new variants of plasmacholinesterase.<sup>145</sup> The variants of plasmacholinesterase are listed in Table I:

<sup>138</sup> A list of these conditions may be found in M. Whittaker, 'Plasma cholinesterase variants and the anaesthetist', *Anaesthesia*, 1980, 35: 174–197. This is an excellent recent review of the clinical aspects of this topic.

<sup>139</sup> P. J. Garry, A. A. Dietz, T. Lubrano, P. C. Ford, K. James and H. M. Rubinstein, 'New allele at cholinesterase locus 1', *J. Med. Genet.*, 1976, 13: 38–42.

<sup>140</sup> H. M. Rubinstein, A. A. Dietz, T. Lubrano and P. J. Garry, ' $E_1^j$ , a quantitative variant at cholinesterase locus 1: immunological evidence', *ibid.*, 1976, 13: 43–45.

<sup>141</sup> H. M. Rubinstein, A. A. Dietz and T. Lubrano, ' $E_1^k$ , another quantitative variant at cholinesterase locus 1', *ibid.*, 1978, 15: 27–29.

<sup>142</sup> The  $E_1^k$  variant was so named in recognition of the work of Kalow in clarifying the recognition and inheritance of the "atypical" allele.

<sup>143</sup> Methods for following the hydrolysis of suxamethonium were available before 1975, but these were time-consuming and difficult.

<sup>144</sup> D. P. Agarwal, S. Schwenkenbecher, L. M. Srivastava, H. W. Goedde, 'Spektrophotometrische Bestimmungsmethode für serumcholinesterase (EC 3.1.1.8) – varianten mit succinylbischolin als substrat', *Z. klin. Chem. klin. Biochem.*, 1975, 13: 133–135.

<sup>145</sup> Goedde and Agarwal, *op. cit.*, note 116 above.

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TABLE I

GENETICALLY DETERMINED VARIANTS OF  
PLASMA CHOLINESTERASE [EC 3.1.1.8]

Name	Symbol	Hydrolysis rate for Suxamethonium	Authors and Date of Discovery
Normal	E <sub>1</sub> <sup>u</sup>	100%	
Atypical [Dibucaine-Resistant]	E <sub>1</sub> <sup>a</sup>	Reduced	Lehmann and Ryan 1956 (104) Kalow and Genest 1957 (105)
Fluoride-Resistant	E <sub>1</sub> <sup>f</sup>	Intermediate	Harris and Whittaker 1961 (117, 118)
'Silent' No enzyme	E <sub>1</sub> <sup>s</sup>	Nil	Liddell, Lehmann and Silk 1962 (125)
V. Low Activity	E <sub>1</sub> <sup>T</sup>	2-8%	Gutsche <i>et al.</i> 1967 (128)
V. Low Activity	E <sub>1</sub> <sup>R</sup>	< 10%	Scott and Wright 1976 (134)
'C <sub>3</sub> '	E <sub>2</sub> <sup>+</sup>	Increased slightly	Harris <i>et al.</i> 1963 (135)
Cynthiana	E <sub>Cynthiana</sub>	Greatly Increased	Neitlich 1966 (136)
<i>Quantitative variants</i>	E <sub>1</sub> <sup>j</sup>	Reduced	Garry <i>et al.</i> 1976 (139) Rubinstein <i>et al.</i> 1976 (140)
	E <sub>1</sub> <sup>k</sup>	Reduced	Rubinstein <i>et al.</i> 1978 (141)
	E <sub>1</sub> <sup>su</sup>	Reduced	Goedde and Agarwal 1978 (145)

*Note:* The hydrolysis rate for suxamethonium observed clinically is altered for E<sub>1</sub><sup>s</sup>, E<sub>Cynthiana</sub>, E<sub>1</sub><sup>j</sup> and E<sub>1</sub><sup>k</sup> predominantly because these alleles cause a change in the *amount* rather than the *activity* of enzyme produced.

The story of suxamethonium apnoea can be continued up to the present day. It was recognized quite early in the analysis of this problem that the prolonged response to suxamethonium was associated with a low level of pseudocholinesterase activity. It was suggested that rather than ventilate until the patient recovered through removal of the drug by excretion, it would be desirable to treat the apnoea by injection of a concentrated preparation of pseudocholinesterase. Such a preparation became available from the Cutter Company of California. It was injected successfully when an individual was actually experiencing prolonged apnoea following injection of suxamethonium.<sup>146,147</sup> However, it was not possible to continue this work, because some of the concentrated preparations proved antigenic, and some may have been contaminated with virus. In 1968, a suitable enzyme preparation became available in

<sup>146</sup> J. Calvert, H. Lehmann, E. Silk and W. K. Slack, 'Prolonged apnoea after suxamethonium - a case study of pseudocholinesterase', *Lancet*, 1954, ii: 354-356.

<sup>147</sup> Lehmann and Simmons, *op. cit.*, note 111 above.

Germany.<sup>148</sup> This was tested and recommended for general use in suxamethonium apnoea. It is commonly used in Germany today.<sup>149</sup> British interest in this problem is now reviving, and the use of enzyme preparations in the treatment of prolonged apnoea may yet become established clinical practice in the U.K.<sup>150</sup>

More work needs to be done on apnoea and its causation – defective enzymes are not the entire story. In a study by Thompson and Whittaker,<sup>151</sup> it was shown that one-third of all the patients in their sample group who had experienced prolonged apnoea were of normal genotype in relation to this enzyme, and had normal cholinesterase activity! It is likely that at least some of these individuals possess variant forms of plasmacholinesterase as yet undiscovered.

The importance of suxamethonium to pharmacogenetics was acknowledged by Kalow, when concluding the First International Conference on Pharmacogenetics in 1967: "some of the topics like ... prolonged action of succinylcholine and slow inactivation of isoniazid have been godfathers to the field of pharmacogenetics".<sup>152</sup>

## 7. OTHER EFFECTS OF SUXAMETHONIUM

I have concentrated on one major side-effect seen with suxamethonium because of its considerable importance in influencing ideas in the fields of genetics and pharmacology as well as in areas of clinical interest. However, apnoea is not the only problem with suxamethonium. In the current edition of Martindale,<sup>153</sup> some thirteen different effects are listed. Some of them are due to the cholinomimetic properties of the drug, e.g., bradycardia.

As a result of depolarizing the end-plate, suxamethonium causes release of potassium from inside the muscle cells into the extracellular space, and thence into the blood plasma. Fortunately, in only a small group of patients – those who have been severely burned, and those who have neurological injuries<sup>154</sup> – has the problem become serious. The risk is that the plasma level of potassium will reach a value high enough to cause cardiac arrest.

In addition, suxamethonium has contributed to legal, as well as medical, history. It was used for a murder, and it is still controversial whether the drug or its breakdown products can be detected in the body of a victim.<sup>155</sup>

<sup>148</sup> H. W. Goedde, K. Altland and W. Schloot, 'Therapy of prolonged apnoea after suxamethonium with purified pseudocholinesterase: new data on kinetics of the hydrolysis of succinylcholine and succinylmonocholine and further data on N-acetyltransferase polymorphism', *Ann. N.Y. Acad. Sci.*, 1968, 151: 742–752.

<sup>149</sup> Goedde and Altland, *op. cit.*, note 130 above.

<sup>150</sup> H. Lehmann, personal communication, 1979.

<sup>151</sup> J. C. Thompson and M. Whittaker, 'A study of the pseudocholinesterase in 78 cases of apnoea following suxamethonium', *Acta genet. Statist. med.*, 1966, 16: 209–222.

<sup>152</sup> W. Kalow, 'Concluding remarks', *Ann. N.Y. Acad. Sci.*, 1968, 151: 1001.

<sup>153</sup> W. Martindale (editor), *The extra pharmacopoeia*, 27th ed., London, Pharmaceutical Press, 1977.

<sup>154</sup> Cf. a recent report indicating that suxamethonium can precipitate ventricular arrhythmias in patients with polyneuropathy: R. J. Fergusson, D. J. Wright, R. F. Willey, G. K. Compton and I. W. B. Grant, 'Lesson of the week: suxamethonium is dangerous in polyneuropathy', *Br. med. J.*, 1981, i: 298–299.

<sup>155</sup> In April 1967, a Florida anaesthetist was convicted of killing his wife with succinylcholine chloride. Respiratory paralysis would occur with a sufficient dose of the drug, and in the absence of artificial ventilation, this would, of course, result in death. In retrospect, the crime seems very elegant, for the hydrolysis of

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Finally, mention must be made of suxamethonium as a pharmacological tool. Curiously, whilst this drug was designed as a synthetic curare compound, its pharmacology is surprisingly different.<sup>156</sup> Unlike curare, it depolarizes the postsynaptic membrane and causes muscle fasciculations (and thus, in some patients, post-operative pain). Suxamethonium, and decamethonium, are as important in the development of new ideas within pure pharmacology as in clinical work. Research on the detailed properties of cholinergic receptors and their "desensitization" properties goes on to this day.<sup>157,158,159</sup>

The above account has shown the history of suxamethonium to be surprisingly complex for a drug that many consider to have been developed by logical consideration of features of the *d*-tubocurarine molecule. There can be little doubt that suxamethonium research made a major contribution to the development of pharmacogenetics in the 1950s. Suxamethonium is now almost a field of its own. Many hundreds of papers have been published about the drug, and since 1957, it has had its own subject heading in *Index Medicus*. It is likely that it will remain in clinical use for some years to come, and that further research into its mode of action and the genetics of plasmacholinesterase will be undertaken.

### SUMMARY

In comparison with some drugs, suxamethonium appears to have had a simple origin. It was developed from the methonium compounds in the late 1940s. These compounds are one family in a group of drugs based on structural features of the *d*-tubocurarine molecule. Whilst the neuromuscular blocking properties, and thus the potential clinical usefulness, of suxamethonium were first demonstrated by Bovet in 1949, a number of earlier workers had made and tested the drug. One of these groups had worked some forty years before Bovet's success. For a variety of reasons, they failed to show its major physiological action.

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the drug, described by Glick, (op. cit., note 61 above), results in succinate and choline – many grams of which are already present in the body. Functionally, the drug seems to disappear without trace.

It is still a matter of debate as to whether it is possible to detect raised levels of the hydrolysis products of suxamethonium, when the dose needed to block respiration is low, and there is likely to be some variation in the levels of choline and succinate present physiologically. In the early 1960s it was thought impossible to detect this drug in the human body. New tests were stimulated by, and devised for, the trial of the anaesthetist. It is the validity of these tests that is currently under attack. Alex Gringauz, *Drugs – how they act and why*, Saint Louis, C. V. Mosby, 1978. (I am indebted to Mr. P. J. Turpin for this reference.) A. Gringauz, personal communication, 1979. *Southern Reporter*, 2nd series, vol. 223, St. Paul, Minn., West Publishing, 1969, pp. 68–76. [Update], 'Coppolino: hopes for vindication', *Newsweek Mag.*, 7 May 1979.

<sup>156</sup> E. J. Zaimis, 'The neuromuscular junction: areas of uncertainty', in Zaimis, op. cit., note 66 above, pp. 1–21.

<sup>157</sup> It has recently been shown that decamethonium acts by opening, and then blocking ion channels. See P. R. Adams and B. Sakmann, 'Decamethonium both opens and blocks endplate channels', *Proc. Nat. Acad. Sci. (U.S.A.)*, 1978, 75: 2994–2998.

In view of the similar pharmacological properties of suxamethonium, it seems likely that it too acts by ion channel blockade. However, this remains to be conclusively demonstrated.

<sup>158</sup> A good guide to the electrophysiological analysis of the action of neuromuscular blocking agents can be found in Colquhoun, op. cit., note 67 above. See also, P. R. Adams, 'Molecular aspects of synaptic transmission', *Trends Neurosci.*, 1987, 1: 141–143.

<sup>159</sup> D. Wray, 'Frequency of opening of channels by depolarizing drugs', *J. Physiol.*, 1978, 284: 149–150.

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The history of suxamethonium after its initial adoption for clinical use is particularly interesting. One side-effect – prolonged respiratory depression – proved to be a very complex problem. Its solution made an invaluable contribution to pharmacogenetics – the understanding of the genetic control of the response of an individual to drugs. The way in which this problem was solved illustrates how the use of certain methods can determine the nature and usefulness of the results obtained.

Suxamethonium has also contributed to the understanding of fundamental mechanisms at the neuromuscular junction. Paradoxically, it is a depolarizing drug, with a mode of action different from that of *d*-tubocurarine despite their common structural features.

ACKNOWLEDGEMENTS

It is a pleasure to thank the following for their guidance and encouragement: Professors H. Blaschko, E. Bülbring, G. Buttle, H. Lehmann, Sir William Paton, and E. J. Zaimis; and Drs. R. B. Barlow, A. F. Brading, E. W. Gill, A. Gringauz, D. B. Hope, T. J. Horder, J. Walker, C. Webster, and D. Wray.

I should also like to thank Mr. R. Moore, Librarian of the National Institute for Medical Research, Mill Hill, for searching the Institute archives on my behalf.