John William Trevan. 1887-1956
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Source: *Biographical Memoirs of Fellows of the Royal Society*, Vol. 3 (Nov., 1957), pp. 273-288
Published by: The Royal Society
Stable URL: http://www.jstor.org/stable/769366
Accessed: 19/05/2009 07:17

JOHN WILLIAM TREVAN

1887-1956

Career

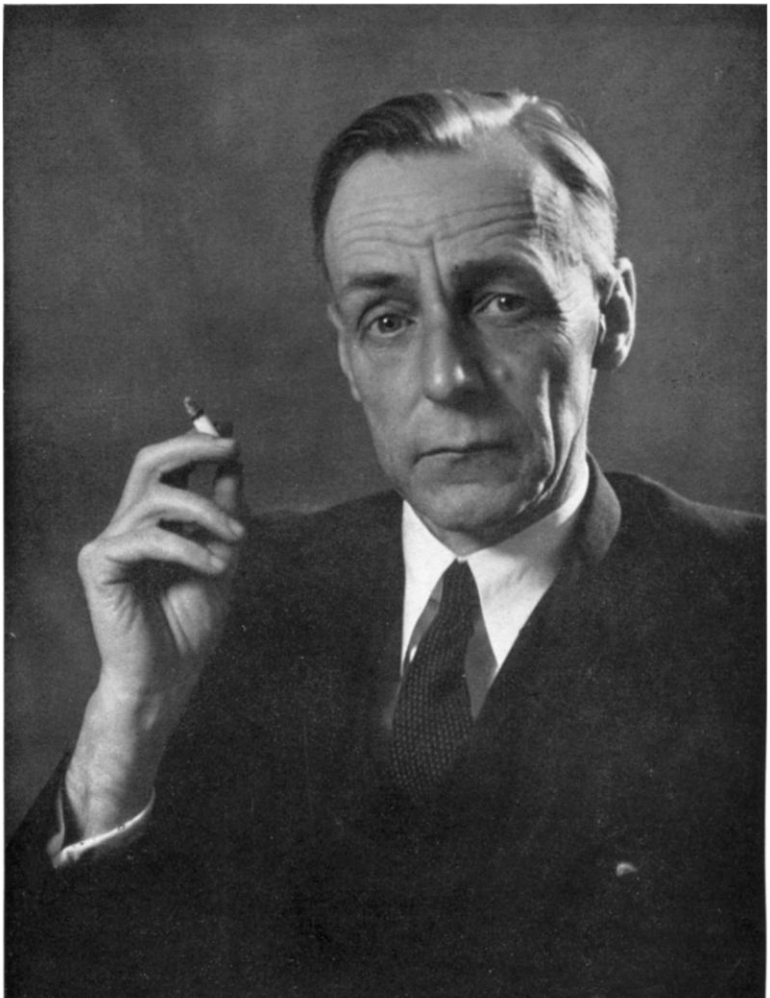
JOHN WILLIAM TREVAN was born on 23 July 1887. His father was John William Stoneman Trevan of Plymouth and his grandfather was another John William Trevan. His father was originally a carpenter, but he was a very intelligent man and in these days he would perhaps have won a state scholarship. As it was he became clerk of works to a large building project and eventually went into business on his own account as a contractor in Plymouth. His wife Bessie Babbage was a simple country woman, but her son always treasured the theory, unsubstantiated by any proof, that he was descended from Charles Babbage, F.R.S., the inventor of calculating machines and one of the founders of the British Association.

The subject of this memoir was born in Bodmin, Cornwall, where his father was helping to construct the railway from Bodmin to Bodmin Road. He was the eldest of three children and had a brother, Jim, now in Canada, and a sister Winifred who has been dead many years.

His parents belonged to the Plymouth Brethren and he was brought up in the rigid practice of their faith. He was not allowed to read anything but religious books on Sundays or to play card games, and he was expected to believe that every word in the Bible was literally true. He was always religious, but in later life he was also broadminded and tolerant.

He went to the Regent Street School in Plymouth where, in spite of his undistinguished career as a diffident boy in a very large class, he was spotted by a master as having good potentialities. On the day of the scholarship examination for the Plymouth Scientific and Technical School (now the Plymouth and Devonport Technical College), when Trevan was fifteen, this master asked him why he was not a candidate. He replied that he had not asked his father, and the master said 'Sit the exam. first and get your father's permission afterwards'. By these words that master did a great service to science.

He attended the Technical School for three years and had the good fortune to be involved in an educational experiment. The school started a serious course of instruction in science when such courses were rare, and among the first fifteen boys to attend, a number besides Trevan became famous, including Professor Herbert Dingle the philosopher, Professor G. Hadfield the pathologist, Sir Lionel Horwill the judge, Mr Norman Lake who was senior surgeon at Charing Cross Hospital and Dr C. L. Williams who



John W. Trevan

became Medical Officer of Health for Barking. This experiment, like other such experiments, was eventually too successful and the classes became overcrowded, but for a few years the atmosphere must have been most stimulating. Chemistry was taught to a high standard by Dr J. W. T. Thackrah, who was quiet and impressive with many little mannerisms which amused the students. Biology was taught by a stimulating man called J. Hodgson who had been biologist to Scott's first expedition in the Antarctic. The students spent their half-holidays collecting plants for him on Dartmoor and specimens from the seashore. Many of them matriculated in London; Trevan and Lake took the preliminary medical examinations in chemistry, physics and biology in 1906, and won scholarships at London hospitals.

Trevan had a brilliant career as a medical student at St Bartholomew's Hospital. He won the junior and senior scholarships, the Harvey prize in practical physiology, the Foster prize in anatomy, the Brackenbury Scholarship in medicine, and the Walsham and Burrows prizes in pathology. He obtained the B.Sc. with honours in physiology in 1908 and the medical qualifications of M.B., B.S. and M.R.C.S., L.R.C.P. in 1911.

He learned clinical medicine as clerk to Sir Wilmot Herringham, who was well before his time in the use of scientific methods of diagnosis. Neither he nor Drysdale, his assistant physician, was in consulting practice and they had plenty of time to develop the laboratory side of medicine. T. S. Hele, G. Graham, A. J. Clark, P. Hamill, J. W. Trevan, E. D. Adrian, R. A. Peters, G. Hadfield, I. de B. Daly, E. B. Verney and many other famous men were all connected with this same firm at different times.

Trevan became house physician to Herringham in 1911. He was never really interested in clinical medicine and was apt to regard each patient as a problem which was not only unsolved but insoluble, but when his colleague Dr P. Hamill went to the war in 1916 he entrusted the care of his father's fibrillating heart to Trevan with complete confidence. Trevan became M.R.C.P. in 1913, but then he plunged into laboratory work because he 'found clinical medicine too difficult'.

From 1912 to 1914 he held a Fishmongers' Company Research Scholarship and did experiments on gastric test meals in which contents of the stomach were ashed in three very valuable platinum bowls. These were left in a safe and Trevan, who was always absent-minded, developed the habit of losing the key.

From 1914 to 1920 he was demonstrator in physiology and casualty physician. The physiological department was run by J. S. Edkins, who was also lecturer at Bedford College, but Trevan was more impressed by F. A. Bainbridge (later F.R.S.), who was lecturer in pharmacology. Langdon Brown, who became senior physician at Bart's and Regius professor of physic at Cambridge, was also in the department and must have been a stimulating colleague.

Trevan thought deeply and was fond of drawing curves on graph-paper and skilled at making apparatus. For example, he used the lead screw of a lathe to drive the piston of a syringe in order to give a constant infusion of digitalis to a cat; a refined form of this apparatus became known later as the micrometer syringe. His first scientific publications were brief accounts to the Physiological Society of work on the kidneys and respiration carried out on behalf of the Medical Research Committee.

During this time Trevan was teaching physiology and he ran the whole department alone for about 12 months at one stage. His lectures, which were carefully prepared, appealed mainly to the clever students, and one of these, F. R. Winton, discovered that they were based on *The principles of general physiology*, by W. M. Bayliss.

In 1917 he joined the army as a Captain and pathologist in the R.A.M.C. and spent an entertaining 18 months in Cairo and Salonika. He was called home, with many others in Christmas 1918 because of the influenza epidemic in Great Britain.

In 1920 Trevan was appointed pharmacologist to the Wellcome Physiological Research Laboratories, which had already become famous through the work of H. H. Dale, G. Barger, P. P. Laidlaw and others. Most of his best work was done there in rooms on the ground floor looking out over the grass at Langley Court, Beckenham. My own first experience of research was under his guidance when he was most active (1925-26). He taught me to do things for myself, and this included making up standard solutions of acid and alkali, and helping in the construction of a static electrometer for measuring pH with a glass electrode. One day when he had lost something and suspected that it had been tidied away by his secretary, he went round muttering 'It's all due to this confounded tidiness. It always leads to trouble. I won't have it in my lab.'

Important early work with sulphonamides and the first experiments with diaminodiphenylsulphone were done by G. A. H. Buttle under Trevan's guidance. In 1941 he succeeded R. A. O'Brien as director of the laboratories and became a member of the Board of the Wellcome Foundation. A. C. White became head of the pharmacological department which inevitably grew as many new types of drug made their appearance.

The laboratories played an active part in the 1939-45 war. They were asked to prepare one million doses of tetanus antitoxin for the forces, and decided to make three million, which was fortunate because the final output reached three and a half million doses.

The manufacture of penicillin presented great difficulties; there was no room for it and no men could be spared for building. Eventually pressure was applied and a number of builders appeared, but it transpired that they had been obtained by releasing patients from a mental hospital!

In 1952 Trevan became Research Director of the Wellcome Foundation, succeeding C. H. Kellaway, and in 1953 he retired from this post and from the board, and was appointed consultant.

He was one of the original 29 members of the British Pharmacological Society when it was founded in 1931 and he became an honorary lecturer in pharmacology at University College London and a member of the Board of Studies in pharmacology in London University. When the Biometric Society was founded he became the first Vice-President of the British region. This international society is devoted to a branch of knowledge which owes much to Trevan and it was entirely appropriate that he should be at the head of the British section of it.

He played an active part in the work of the Research Defence Society; he served on the council for many years and was Chairman at the time of his death. 'To difficult and often delicate negotiations, he brought a great scientific reputation, complete personal integrity, and a serenity of outlook which disguised a firmness of will. Sure in his facts, he was a skilful and successful negotiator. Always fair and respecting the view of his opponent he knew when to call a halt.' (*Conquest*, **45**, 12, 1957).

He became a governor of St Bartholomew's Hospital Medical School (1937), Fellow of the Royal College of Physicians (1942) and President of the Section of Therapeutics and Pharmacology of the Royal Society of Medicine (1943). He served on the Biological Standards Commission of the League of Nations, on various committees of the British Pharmacopoeia Commission connected with biological standardization and on committees of the Medical Research Council and the Agricultural Research Council.

He was elected F.R.S. in 1946 and became Chairman of Government Grant board H.

He died suddenly and unexpectedly of coronary occlusion while he was working in his garden on 13 October 1956, at the age of 69. He had just promised to be press editor of the *British Journal of Pharmacology*. This would have involved much work and he must therefore have been feeling full of energy.

He left a widow and eight children, two of whom qualified in medicine, after following their father as students at Bart's.

Home life

When he was a boy he was fond of messing about in boats in Plymouth harbour and on the river and going for long walks and bicycle rides with his brother and school friends over Dartmoor. He often used to spend part of his holidays driving round Devonshire in a pony trap with a family of girl cousins from Paignton, who thought him dreamy and quiet; in later years these adjectives would not have been appropriate. He had an abiding affection for the West Country and he was very fond of talking about it. He used to boast that he had played bowls on Plymouth Hoe.

When he first came to London in 1906 he lodged with Mr and Mrs Percy Keys in Camberwell. They were zealous Baptists and it was thought that they would safeguard him from the evils of the metropolis. However, it was through them that he met and became engaged to Ida Kathleen Keys, the youngest daughter of the Rev. J. L. Keys, who was a Baptist minister and a cousin of Percy Keys. His parents opposed the match on religious grounds and the engagement lasted seven years. They were married in June 1916 after his father's death, and he was excommunicated by the Plymouth Brethren for marrying outside the sect. He was very sorry about this, but he did not let it rankle, and it did not dim his religious faith.

He lived for many years with his mother-in-law and her sons and daughters in a house in Grange Road, Upper Norwood, and his 3 sons and 2 daughters by his first wife were born there. When old Mrs Keys died he brought his own mother to live with them, too. Later he bought the house next door and lived there with his family until it was destroyed by bombs in October 1940. His wife became ill with cancer in the summer of 1937 and died at the end of that year and his sister-in-law came to live with them and looked after the children.

In September 1939 Trevan married Margaret, eldest daughter of Sir Hubert and Lady Llewellyn Smith, who had worked under him at Beckenham years before. They were married about an hour after the outbreak of war and spent most of their wedding night in an air-raid shelter. He was slightly wounded in the arm when his house was destroyed by bombs in 1940 but no one else was hurt. The family then moved to another house in Upper Norwood where they lived for 12 years. There were 2 daughters and a son by the second marriage and they moved in 1953 to a beautiful old rambling house with low ceilings and heavy beams in Woodside Green near Croydon. He was very fond of this place and became an enthusiastic gardener.

Trevan was a man of moods. Sometimes he was depressed and gloomy, but more often he was full of boyish enthusiasm. When the laboratories acquired a motor mower he tried it out himself and was seen seated upon it driving round the cricket field with a grin of beaming satisfaction on his face. He had an enormous zest for life and preferred to run rather than walk; to his death he always ran upstairs. He was interested in people, their schemes, ideas, and problems, and always ready to help them. He was fascinated by wild birds and flowers and loved trying to identify them. He was an omnivorous reader and remembered most of what he read. He said of himself, 'My relaxations have been at various times playing the piano, singing in church choirs, badminton, lawn tennis, cricket, hockey, chess and sailing, all performed with wild enthusiasm and devastating incompetence. But my experience leads me to believe that "rabbits" get more fun than the experts. The only hobby at which I have been any good has been the acquisition of miscellaneous information about anything in which a man can be interested.'

He loved motor cycling and after the first world war he rode a highly dangerous machine—an A.B.C. with a Sopwith engine, which had a spectacular acceleration up to 80 m.p.h. He used to wear a bowler hat for motor cycling, partly to protect his head in case of accidents, and partly because the police would be unlikely to think that a man wearing a bowler hat could be exceeding the speed limit. He once had a specially interesting skid on the ice in Croxted Road when he and the bicycle, both rotating on their axes, rotated about one another on the road and, he said, prompted some interesting reflexions on the dynamics of the origin of the solar system, even before he came to rest. Later he became devoted to second-hand cars to which he used to give first-aid with copper wire and other effective but unconventional materials. He was fond of touring on the continent, and once in early Nazi days he was in Rothenberg with a car and had finished lunch when a large German came up and said without any preamble, 'Sir, you have the best type of English face—honest and intelligent'. It was an odd compliment, but it pleased Trevan.

He was very youthful in spirit and had great sympathy for young people and their doings: at one time he was a Sunday school teacher. Before he had a family of his own he would spend his spare time taking young people to Maskelyne and Devant's or to concerts or museums or to the Royal Institution. Later he was deeply attached to his own family, as they were to him, and he gave them fully of his love, sympathy, help and encouragement. He loved parties, especially if they involved singing or dressing up for charades. He invented a variant of badminton for the children to play in the garden and called it 'goodminton'. He never minded making himself ridiculous and was fond of telling tales against himself.

He was gloriously absent-minded. During the war he used to bring home horse meat for the dog, but often the meat would stay in the back of the car all over a hot weekend to be carried back to Langley Court with its odour on Monday morning. After a bit his secretary used to tell Mrs Trevan by phone when horse meat was coming.

Once when he had been attending a meeting of the Board of the Wellcome Foundation he came out down a corridor whistling. The porter, not recognizing him, said 'Young man, please do not whistle so loudly. The directors are holding a board meeting.' 'That's all right', he said, 'we've finished our meeting.'

There was once a clergyman who went to visit the Bethlehem Mental Hospital in Park Langley and turned up in the Wellcome Laboratories by mistake. Dr Trevan came out of his room running and singing 'Rock of Ages'. The clergyman asked the receptionist 'How long has he been here?' and did not seem surprised when he was told 'A very long time'.

He enjoyed fun and games to the full, but he had the faculty of suddenly and completely detaching himself from his surroundings if an idea occurred to him. Out would come pencil and paper and usually a slide rule, or he would pick up a book and forget his surroundings for a time, and then quite suddenly he would look up, push his glasses on to his forehead and with a charming apologetic grin he would be back in the world again. He liked using graphical methods, but was prepared for more exact calculations when necessary. He once said, 'I do wish people would not use groups of six mice. They involve me in pages and pages of recurring decimals.'

He made thoughtful contributions to scientific discussions in a humorous and informal way which tended to conceal their importance. He was so ready to help others that he did not have enough time for his own work. His desk was always full of the results of experiments which he had performed with care but which he did not consider worth publishing. At the same time he devoted much effort to advising his younger colleagues about their experiments and about their publications. He had an encyclopaedic knowledge of medical science and his advice was always worth having, but he did not hesitate to express himself emphatically to make his points. 'My dear ass', he would say, 'You've got this all wrong', and the subsequent discussion was all great fun.

He was very fond of music. After a few hours' work as a student he would start playing extracts from Wagner's operas arranged for the piano. He was a determined rather than an expert performer and when he had mastered the Wagnerian chords he struck them in no uncertain manner. Later on he took delight in accompanying his family when they sang or played the oboe, 'cello or violin. He especially enjoyed playing duets on the piano and he would sometimes look up with an air of triumphant surprise when he finished at the same moment as his fellow performer.

He used often to slip into the church for an hour's playing on the church organ, of which he thoroughly understood the workings and to which he would render first-aid if some small thing went wrong. He also sang bass in the choir.

He dreaded responsibility, but never ran away from it. He was no respecter of persons and would stand up to the most eminent authority if he thought he was right and the authority wrong. He always stood for scientific and ethical truth against commercial expediency.

He was a very religious man. When he first came to London he continued to attend meetings of the Plymouth Brethren until his marriage. He then attended the local Baptist church, but after 7 years transferred his allegiance to St Aubyns Congregational Church, Upper Norwood. At a service in this church on 18 October 1956, the Reverend Norman Castles, M.A., paid him a moving tribute from which the following words are taken:

'The name "Trevan" for many years has been an integral part of this church. At his death John Trevan was a Deacon, a member of the Choir and a regular worshipper Sunday morning and Sunday evening. He had served as a leader in the Sunday School, as a Sidesman and as a Fabric Steward. But his real service was just himself, his charming personality, his complete dedication to the church and his many-sided accomplishments. He used to set a shining example by sitting with his sons and daughters in the body of the church and he had the great joy of seeing the older members grow to manhood and womanhood maintaining the family religious tradition. . . .

'Here in this church he came among us as an equal, conscious with us of the need for self-examination for refreshment of spirit and the religious duty of thanksgiving to God for all his goodness. In the Choir Vestry, before service, he would often lead us in prayer by saying the General Thanksgiving.

Each time you were made to feel that every word of gratitude in that comprehensive and incomparable prayer was the outpouring of John Trevan's own heart and mind to God. . . .

'But no tribute to John Trevan would be complete which did not recall his youthful buoyancy and his exuberant spirit. He had a puckish smile and a keen sense of humour. He loved to tell stories about himself, about his absent-mindedness, his unconventionality, his wit capped by a greater wit. He was never so happy as when he was at a party in his home or at a social in the Church. He delighted to be a character in a play, to dress up for a Choir chorus or to join in a nonsensical game. His versatility was an unending pleasure.'

Work

While Trevan was working in the department of physiology at Bart's he became interested in the respiratory centre. He divided the brain stem at various levels in cats and came to the conclusion that respiration was not controlled by a single centre but by a chain of neurones (1916). Later, with Miss Boock at Beckenham (1922), he observed great gasps of inspiration when the section was just below the colliculi, and concluded that a primitive respiratory centre below this level was normally under the control of a higher centre just above it. This work was overshadowed by the more detailed work of Lumsden (1923).

W. H. Hurtley was collecting evidence that many of the symptoms of diabetic ketosis were due to the presence of acetoacetates in the blood. He and Trevan (1916) therefore carried out experiments in cats which showed that acetoacetates increased the ventilation. They observed similar effects with acetylacetone and with salicylates, and suggested that all these substances owed their action to the presence of the group C(OH):CH. The stimulant action of salicylates on the respiration is now well recognized, but these early experiments on it and the ingenious suggestion that it is related to the hyperventilation of diabetes have been forgotten. Trevan also observed that acids in the blood, and these other chemicals, acted on the higher respiratory centre, and lost their stimulant action when the brain stem was divided just below the colliculi.

In 1921 Trevan and Ellen Boock published an interesting study of the effect of paraldehyde on the respiration. They plotted the ventilation in decerebrate cats against the pH of the blood, which was altered by giving varying amounts of CO_2. In the absence of an anaesthetic apnoea occurred with hyperventilation at about pH 7·7, and the ventilation increased rapidly as the pH fell. Under the action of paraldehyde the respiratory centre became insensitive to changes of pH so that not only did a fall of pH have less stimulant effect, but also a rise of pH was less liable to cause apnoea; eventually the ventilation became independent of the pH and the results were represented by a horizontal line.

In 1918 Trevan published a paper on the viscosity of the blood. After discussing various sources of error and precautions against them, he described experiments which showed that when the corpuscular volume was constant the viscosity of whole blood was proportional to that of its plasma, and that the effect of changes in the corpuscular volume was governed by a theoretical formula proposed by Hatschek.

During the early years at Beckenham Trevan devised several ingenious pieces of apparatus—a frontal writing point for use with ink, a microbalance and the micrometer syringe. The microbalance (1926) is a cheap, simple and sturdy deflexion balance in which a horizontal steel wire is fixed at one end and depressed by weights at the other end. The depression is measured by adjusting a micrometer screw to touch the end of the wire and weights of 1 to 30 mg can be weighed in 30 s with an accuracy of about $\pm 0 \cdot 01$ mg. This device has been found useful in pharmacological laboratories for weighing out drugs for an experiment. It has the same functions as a torsion balance, but is cheaper and can easily be adjusted to other ranges of weight by changing the wire.

In the micrometer syringe (1922, 1925) the piston of a small glass syringe is controlled by a micrometer screw and small volumes can be measured with a standard deviation of about 0·2 cubic millimetres, so that titrations can be made with an error of 0·2 per cent when the total volume used is only 0·1 ml. The same principle had been used by Kelvin and Lister, but Trevan did not know this until after he had designed a compact and convenient instrument which was manufactured by Burroughs Wellcome and Co, and has been very widely used all over the world. One of its first applications was a method for estimating calcium in blood serum (Trevan & Bainbridge 1926) by a modification of the method of Kramer & Tisdall using only 1 ml of serum, or even 0·1 ml if great accuracy was not essential.

At about this time Trevan and Boock studied various problems which arose in connexion with the routine work of the laboratories. Frogs which had become pale after exposure to light were more easily killed by digitalis than frogs kept in the dark. When frogs were made pale by the injection of adrenaline, or dark by the injection of posterior pituitary extracts, the effects of digitalis showed the same correlation with the colour of the skin. Hogben & Winton had suggested that the effect of light on the colour of the frogs' skin was actually due to the release of hormones from the frogs' adrenals and pituitaries. The new results were 'at least not in contradiction with this view'.

Glenny & Allen had shown that an epizootic among guinea-pigs could be controlled by changing the diet and Boock & Trevan investigated the factors involved. They showed that the original diet of grain and mangolds was deficient in vitamin A so that the guinea-pigs might suffer from keratomalacia, which was cured with cod-liver oil. For satisfactory growth it was also necessary to add calcium and caseinogen to the diet. The importance of vitamin D was not generally recognized at that time (1922) and its possible effects do not enter the discussion. The effects of caseinogen may perhaps have been due to vitamin B_{12}, but this was not known till many years later. The authors drew carefully worded conclusions and cannot have regretted what they said.

In 1927 Trevan & Boock made a quantitative study of the effect of pH on the activity of local anaesthetics. Gross had found that the effects of these drugs were increased by alkali and suggested that they were due to the free undissociated base. Regnier, on the other hand, had explained this phenomenon as an effect on the tissues. In the absence of quantitative data both explanations were valid, and it is now known that both types of effect may occur. Trevan & Boock instilled buffered solutions of various local anaesthetics continuously into the eyes of rabbits for 10 minutes and showed that this produced a change in the pH of the aqueous humour. They measured the threshold concentration and when they plotted its logarithm against pH they got a series of parallel straight lines for all the drugs tested except two. The line for conessine had double the slope of the other lines and this was explained by the fact that conessine is diacidic. The line for benzyl alcohol had no slope at all and benzyl alcohol does not dissociate. These facts confirmed the theory of Gross, but the slopes of the lines were somewhat less than that predicted by the simplest possible theory. Trevan & Boock discussed the reasons for this discrepancy and came to the conclusion that it was not due to a local anæsthetic action of the ions of the drugs, but to a difference between the final pH of the cornea and that of the applied buffer solution. The p*K*s of those drugs was determined with the micrometer syringe using a volume of about 0·03 ml.

Trevan & Buttle (1927) made a joint study of the actions of bacterial toxins in acute experiments. They tested the action of the toxin of *Vibrion septique* on rabbits uterus and other tissues suspended in salt solutions with their movements recorded on smoked drums. In concentrations similar to those occurring in the blood of a rabbit recovering from an average lethal dose, this toxin caused prolonged contractions of the uterus. The effect was reversible on washing and specifically antagonized by the appropriate serum. This fact could be used to titrate the toxin against the serum, and some quantitative data on the amounts of toxin neutralized by various concentrations of serum were obtained. *Bacillus welchii* toxin caused similar effects. When the uterus was exposed to small doses of either toxin it became insensitive to larger doses of both toxins. When rabbits were immunized with *V. septique* toxin their uteri were still sensitive to the toxin *in vitro*. The desensitization which was observed to occur *in vitro* was thus clearly quite a different phenomenon from the immunity which could be produced *in vivo*.

Trevan's most important contribution to knowledge was work which led to the use of statistical methods in pharmacology. His own informal account of how this started is as follows: 'In the early days Burroughs Wellcome insulin was tested not only at Beckenham but also in the National Institute for Medical Research. Some batches of insulin which I passed for potency were rejected by the Institute. This touched my pride (besides getting me into trouble with B.W. and Co). In actual fact neither the Institute nor Beckenham was right; neither of us had really done an adequate assay. So I got out an old *Encyclopædia Britannica*, and spent several weekends "mugging up" statistics from Edgeworth's article on the subject. This eventually resulted in a publication which brought some sort of order into the existing chaos of biological assay, and which was the stimulus to a great deal of work by others which has elevated biological assay to the rank of a science.'

Many people were vaguely aware at that time that different animals of the same species did not always give exactly the same response to drugs, but it was tacitly assumed by most workers in this field that the differences between different animals of the same species were small and could be neglected. The toxicity of drugs was therefore determined by giving a series of different doses each to one animal, and recording the 'minimum lethal dose' actually observed in this way; it was generally believed that this dose would kill all 'normal' animals and that smaller doses would kill none. Discrepant results were explained on the theory that some of the animals were not 'normal'. Shackell had plotted the percentage mortality caused by drugs against the dose and obtained S-shaped curves, but the logical consequences of these observations were neglected, until Trevan proposed that toxicity should be defined in terms of the dose causing a given percentage mortality. He used the term LD50 (or, for example, LD90) to denote the dose killing 50 (or 90) per cent of the animals, and this convenient notation has been generally adopted all over the world.

Trevan collected a number of examples of dose-mortality curves and discussed their significance and interpretation in a famous paper published in 1927 in the *Proceedings of the Royal Society*. Shackell had pointed out that a dose-mortality curve could be regarded as the integral of the frequency distribution of the doses just necessary to kill each individual animal. Trevan calculated the distribution of these 'individual lethal doses' in various actual cases by graphical differentiation of experimental curves and found them positively skew, but did not at first realize that this skewness could be avoided by using a logarithmic scale of doses. He calculated the mean, mode and median of these distributions and after some discussion came to the conclusion that the best dose to measure was the median lethal dose—the LD50. Using the expression $\sqrt{(pqN)}$ for the standard deviation of the observed mortalities and various values of N (number of animals), he calculated in actual cases (*a*) the range of doses which would be expected (with a given probability) to cause a given mortality and (*b*) the range of results which would be obtained by injecting the LD50 and then estimating from the observed mortality by means of the curve what the dose had been. In the case of cocaine this method of calculation from the curve appeared to be justified by the fact that the shape and position of the curve seemed to be practically constant; the calculations then gave an estimate of the error. A general formula for this error was obtained by taking a straight line as an approximation to the dose-mortality curve.

In the cases of diphtheria toxin and insulin the position of the dose-mortality curve varied, but its shape remained approximately constant, in the sense that curves obtained on different occasions could be made to coincide by an appropriate choice of the scales of doses. In this sense the shape of the curve seemed to be characteristic of the drug and the other conditions of the experiment, and the curves were therefore called 'characteristic curves'. It was clear that in these cases accurate assays would involve a comparison of the unknown with a standard preparation. This could be done either by using several doses of each drug and plotting two curves, or by using one dose of each drug and converting the observed percentages into a dose ratio by means of a standard curve. The latter method was simpler and was found to give satisfactory results when used on a large scale for the assay of insulin by estimating the percentage of mice showing hypoglycaemic symptoms. This had then recently become an important commercial problem, and both for the sake of the patients and for the sake of those who bought and sold insulin accuracy was essential. This involved the use of unprecedented numbers of mice and there was a mild sensation when the figures were published. Reporters invaded the laboratory and failing to get satisfactory interviews with members of the staff, published accounts of imaginary interviews, with obviously inaccurate circumstantial details.

Assays using 27000 mice provided the data for calculations which showed that the use of a standard curve gave accurate assays and that the errors observed in practice agreed well with those calculated theoretically. In each assay 30 mice received the unknown and 30 mice received the standard preparation and these assays were repeated about 20 times on each of 12 batches of insulin. The standard deviation of a single assay was calculated directly as 12·65 per cent and indirectly from the shape of the curve as 12·45 per cent. The standard deviation for the mean result on each batch would therefore be less than 3 per cent. and the scientific world was astonished that such accurate assays were possible.

Methods of assay have been developed since that time which have the theoretical advantage that they do not depend on the assumption that the slope of the curve is constant, but Trevan showed that his method did actually give the results which his theory predicted. The success of these calculations was aided by the fact that large numbers of animals were used, and by the fact that, in most of the experiments, the result could be quite accurately predicted, so that the observed mortalities with the unknown and standard preparations must have been almost equal. This success was however a striking demonstration that pharmacological experiments could give results with an error which was not only reasonably small but also measurable. Trevan had not only shown that animals varied more than had been supposed; he made this variation the basis of accurate experiments.

These methods were also applicable in other fields, and during the next few years Trevan applied them to cardiac glycosides, immunology and chemotherapy. In assays of preparations of strophanthus and digitalis in collaboration with J. H. Burn and others he used characteristic curves which were assumed constant, but in 1928 he also used a method suggested by Krogh in which the mortality was plotted against log dose and the results fitted with straight lines. The use of a logarithmic scale was clearly convenient, since different preparations gave curves of similar shape at a constant horizontal distance from one another and this device has formed the basis of many later developments. It gave results agreeing well enough with the results calculated from characteristic curves.

In the same paper (1928) he briefly described two new methods of standardizing digitalis preparations by their action on isolated rabbit's auricle and by their effect when infused slowly into a vein in a frog with a micrometer syringe. Since digitalis contains a number of active principles in different proportions it was not surprising that the various different methods gave different results.

In 1929 Trevan wrote a paper applying similar methods to the assay of antidysentery sera. A standard dose of toxin was injected and the assay was based on the relation between the dose of serum and the percentage survival rate. A logarithmic scale of doses was used and a new formula was given for calculating the accuracy of the result. The flatness of the curve was calculated in terms of the quantity A which, in a later notation, is approximately equal to 35λ. A formula was also given for calculating the error of the estimate of A. In this kind of test, where the animals are used to estimate the excess toxin which has not been neutralized, the percentage error of the assay should be less when the doses of both toxin and antitoxin are increased. Trevan drew attention to this theoretical conclusion and quoted evidence that it was true.

Later in the same year he published a paper, based on the work of his colleague, H. J. Parrish, dealing with the assay of antipneumococcus serum by its effect on the survival rate of mice infected with living pneumococcus. When the survivors were counted at a standard time, similar methods were found to give satisfactory results, but the accuracy could be improved by basing the calculations on the relation between the dose and the survival time. In this case the number of animals for a given accuracy was approximately halved; later work has led to the theoretical conclusion that this is likely to be always approximately true, when quantal data are replaced by measured data. When the dose of the infecting culture (C) was increased the protection could still be obtained by increasing the dose of serum (S), and over a certain range these two quantities were connected by the formula $S=C^{0\cdot32}$. In these experiments, however, unlike those with dysentery toxin, the accuracy of the result did not increase very much when the doses were increased.

In 1931 Trevan applied similar principles to chemotherapy. W. H. Gray had been studying the chemistry of various antimony compounds used in the treatment of kala azar. With the collaboration of Miss H. W. Bainbridge and Miss A. P. Attwood, he tested the effects of some of these compounds in the treatment of mice infected with trypanosomes. If given as a single dose at the appropriate stage of the infection, these drugs caused the organism to disappear for a number of days from the blood and increased the survival time of the mice, but eventually the organisms reappeared and the mice died. Single doses of each were compared with single doses of stibamine glucoside, which was used as a standard, and the therapeutic effect was estimated from the survival time. If the survival times did not differ significantly, the chosen doses were considered equivalent, and if the survival times differed the experiment was repeated with fresh doses until the difference in effect was not significant. In this way it was possible to distinguish doses differing from one another by about 30 per cent, so that the accuracy was sufficient for practical purposes.

In order to measure the toxicity of these antimony compounds larger doses were given to uninfected mice and the relation between dose and mortality determined. It was found that if logarithms of doses were plotted against mortality most drugs gave curves indistinguishable from the integral of a normal frequency distribution. This important conclusion is now generally accepted as true and much of probit analysis is founded upon it. In this paper he also discussed the use of the term 'maximum tolerated dose' which was used to mean the maximum dose which had never been observed to cause death. He pointed out that this depended on the number of animals used and proposed a more precise definition.

A collaborative experiment on the toxicity of aconite (1932) showed that the susceptibility of different colonies of mice varied significantly and emphasized the necessity of basing all experiments on a direct comparison of the unknown with a standard preparation.

Trevan wrote two papers (1934, 1938) in collaboration with G. A. H. Buttle and T. A. Henry on the effect of cinchona alkaloids and allied substances in canaries infected with malaria (Roehl's test). The effects of the drugs were measured in terms of the delay in the onset of the infection, as measured by the appearance of parasites in the blood. A standard dose of quinine was always used and the ratio of the effect of the drug to that of quinine was calculated. This 'quinine ratio' did not of course measure the potency, but it arranged the drugs in order of potency which was all that was then necessary.

In 1939 Trevan wrote a paper on amphetamine, in which he described some experiments on analeptics by a technique which has become popular in more recent years. Mice were anæsthetized with paraldehyde and the duration of the anæsthesia was measured as the time until they began walking about, which was called the walking time. This might vary over a ten-fold range among mice receiving the same treatment and Trevan took the median time, in preference to the mean time, as a measure of the effect. This time was shortened by three types of drug, typified by amphetamine, ephedrine, and picrotoxin, the actions of which could be distinguished by observing the mice.

In 1946-1951 Trevan wrote several papers on the pharmacology of curare. With G. A. Mogey and P. A. Young he studied the assay of curare by its effect on the isolated diaphragm of a rat (Bülbring's method). The paralytic effect of curare on this preparation was found to be very constant and the dose-effect curve was very steep so that when sixteen responses were measured that part of the error of the final estimate of potency which was due to variations of the response was sometimes less than 1 per cent. In these circumstances the usual assumption that errors of measurement of the dose and of the volume of the bath are negligible may not be justifiable unless special care is taken.

Trevan gave a general account of his views on curare and allied drugs in the Bertram Louis Abrahams lecture to the Royal College of Physicians (1951).

He summed up his own work by saying that he had had the satisfaction of starting a number of hares most of which had finally been caught by others. It may perhaps be added that he was always willing to let others have the credit even when he was in at the death himself and, of course, some of the hares are still at large.

I am much indebted to many people who have helped me write this memoir, and especially to Mrs Trevan, Mr Ernest Freeman, Dr Graymore, Dr A. C. White and the writers of various obituary notices.

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BIBLIOGRAPHY

1913 (With W. P. HERRINGHAM.) The localization of function in the kidney. *Quart. J. Med.* **6**, 505.
1914. The estimation of rennin in gastric contents. *Trans. Internat. Congr. Med. London IIIa Chem. Pathol.* p. 23.
1915. Dilatation of the heart. *St Bart's Hosp. J.*, **23**, 18.
1916. The excretion of acid by the kidney. *J. Physiol.* **50**, 15P.
1916. The control of respiration by the mid brain. *J. Physiol.* **50**, 43P.
1916. (With W. H. HURTLEY.) The physiological action of acetoacetic acid and related substances. *J. Physiol.* **50**, 49P.
1917. (With F. A. BAINBRIDGE.) Some actions of adrenalin upon the liver. *J. Physiol.* **51**, 460.
1918. The viscosity of blood. *Biochem. J.* **12**, 60.
1920 Some notes on relapsing fever. *St. Bart's Hosp. J.* **27**, 6.
1921. (With E. BOOCK.) The action of anaesthetics on the respiratory centre. *J. Physiol.* **54**, 131P.
1922. (With E. BOOCK.) The effect of section of the vagi on the respiration of the cat. *J. Physiol.* **56**, 331.
1922. An apparatus for the measurement of small quantities of fluid. *Lancet*, **i**, 786.
1922. A new frontal writing point for use with ink. *J. Physiol.* **57**, 17P.
1922. (With E. BOOCK.) The food value of mangolds and the effects of deficiency of vitamin A on guinea-pigs. *Biochem. J.* **16**, 780.
1923. (With E. BOOCK.) The effect of light on the response of frogs to drugs. *Proc. R. Soc. Med.* **16**, 8.
1923. (With H. W. DUDLEY and P. P. LAIDLAW and E. M. BOOCK.) The effect of insulin on the respiratory exchange. *J. Physiol.* **57**, 47P.
1925. The micrometer syringe. *Biochem. J.* **19**, 1111.
1926. A modification of the deflection balance for use in biochemical laboratories. *Biochem. J.* **20**, 419.

1926. (With H. W. Bainbridge.) The estimation of calcium in blood serum. *Biochem. J.* **20**, 423.

1926. (With J. H. Burn.) The standard for the biological assay of strophanthus. *Pharm. J.* **117**, 439.

1926. (With E. Boock.) The standardization of insulin by the determination of the convulsive dose for mice. *League of Nations Health Organization Document.* Ch. 398, 47.

1927. (With E. Boock.) The relation of hydrogen ion concentration to the action of local anaesthetics. *Brit. J. Exp. Path.* **8**, 307.

1927. (With G. A. H. Buttle.) The action of *Vibrion septique* and *B. welchii* toxin on isolated organs. *Brit. J. Exp. Path.* **9**, 182.

1927. The error of determination of toxicity. *Proc. Roy. Soc.* B, **101**, 483.

1927. The medical aspects of the alkaloids. *Ann. appl. Biol.* **14**, 537.

1928. (With E. Boock, J. H. Burn and J. H. Gaddum.) The pharmacological assay of digitalis by different methods. *Quart. J. Pharm.* **1**, 6.

1929. A statistical note on the testing of anti-dysentery sera. *J. Path. Bact.* **32**, 127.

1929. (With W. Culhane, H. P. Marks and D. A. Scott.) Observations on insulin. Part 2. Physiological assay of crystalline insulin. *Biochem. J.* **23**, 384.

1930. The accuracy of titration of anti-pneumococcus serum. *J. Path. Bact.* **33**, 739.

1931. (With W. H. Gray.) Experiments on antimony compounds used in the treatment of bilharzia disease and kala-azar. *Trans. R. Soc. trop. Med. Hyg.* **25**, 147.

1931. (With W. H. Gray and H. W. Bainbridge.) The ureides of *p*-aminophenylstibinic acid. *Proc. Roy. Soc.* B, **108**, 54.

1931. The physiological action of some toxins. In *System of bacteriology in relation to medicine.* **5**, 194. Medical Research Council.

1932. (With W. A. Broom, J. H. Burn, J. H. Gaddum, and S. W. F. Underhill.) The variation in the susceptibility of different colonies of mice towards the toxic action of aconite. *Quart. J. Pharm.* **5**, 33.

1934. (With H. Paget and A. M. P. Attwood.) The irritant constituent of anti-leprotic oils. *Internat. J. Leprosy*, **2**, 149.

1934. (With G. A. H. Buttle and T. A. Henry.) The action of the cinchona and certain other alkaloids in bird malaria. II. *Biochem. J.* **28**, 426.

1936. Comparison of the proposed new international (crystalline) standard insulin with the current international standard. *League of Nations. Quart. Bull. Health Organization*, **5**, 622.

1938. (With G. A. H. Buttle, T. A. Henry, W. Solomon and E. M. Gibbs.) The action of the cinchona and certain other alkaloids in bird malaria. III. *Biochem. J.* **32**, 47.

1938. The introduction of new remedies into clinical practice. *Proc. R. Soc. Med.* **31**, 267.

1939. (With H. Paget and A. M. P. Attwood.) The irritant action of some drugs derived from hydnocarpus oil. *Int. J. Leprosy* **7**, 167.

1939. Benzedrine: uses and abuses. *Proc. R. Soc. Med.* **32**, 391.

1941. (With R. G. Macfarlane and A. M. P. Attwood.) Participation of a fat soluble substance in coagulation of the blood. *J. Physiol.* **99**, 7P.

1946. The international standard and unit for penicillin. *League of Nations. Bull. Health Organization*, **12**, 214.

1946. Curarine. *Lancet*, **ii**, 361.

1948. (With G. E. Glock and G. A. Mogey.) Pharmacology of some bis-tri methyl-ammonium compounds. *Nature, Lond.* **162**, 113.

1948. (With G. A. Mogey.) Response of the phrenic nerve of the rat to rectangular pulses of direct current. *J. Physiol.* **107**, 28P.

1949. (With G. A. Mogey and P. A. Young.) The assay of d-tubocurarine chloride on the isolated rat diaphragm. A statistical examination. *Analyst*, **74**, 577.

1950. (With G. A. Mogey.) D-tubocurarine salts and derivatives. *Brit. med. J.* **ii**, 216.

1950. (With W. Neilson Jones.) Preservation of fungal sporophores. *Nature, Lond.* **165**, 692.

1951. Curare and curari-mimetic substances. Bertram Louis Abrahams lecture. *Sci. Progr. Twent. Cent.* **155**, 401.