OBITUARY NOTICES.

HORACE EDWARD BROTHERS.

1863—1944.

Horace Edward Brothers died at his home at Old Colwyn on July 3rd, 1944, in his 81st year.

He was a son of the late Alfred Brothers of Manchester, a pioneer of astronomical photography, whose photographs of the solar eclipse at Syracuse in 1870 showed that the corona is an appendage of the sun.

Brothers received his early education at Alderley Edge, and at Chorlton High School, Manchester. From 1881 to 1885, he attended Owens College, studying chemistry under Roscoe and Schorlemmer, and physics under Balfour Stewart. He took a new course of studies specially designed to qualify for a technical position in industry at a time when the employment of scientifically trained men by manufacturers was rare. From 1885 to 1899 he was analyst and technical manager of a chemical works in the Potteries, engaged in the extraction of cobalt and nickel and their compounds, and in the manufacture of borax and boric acid.

In 1899 he became one of H.M. Inspectors of Factories, and in 1903 was deputed to investigate chemically the means of ventilation, and effects of artificial illumination in workrooms in the flax and jute works in Scotland. He also took part in a special enquiry into the dangers peculiar to chemical industry, and the most effective means for prevention of accidents to workers in these factories. The enquiry led to the drawing up of a code of " Regulations for Chemical Works " issued by the Home Office Factory Department in 1922. These Regulations still prove effective, and many of their requirements have been embodied in the new Factory Act of 1938.

Brothers retired from the Civil Service in 1925. He was a Fellow of the Royal Institute of Chemistry, a Fellow of the Chemical Society for nearly 60 years, and a life Member of the Society of Chemical Industry. He was a joint author of a paper on phenolic constituents of blast furnace tars published in the *Journal* in 1886.

(Miss) D. M. Brothers.

DAVID GWYNNE DAVIES.

1907—1944.

David Gwynne Davies died in tragic circumstances at Malvern on April 16th, 1944. He was the only son of Mr. J. R. Davies, sometime Headmaster of Dowlais Boys' School, Merthyr Tydvil, and was educated at his father's school and at Merthyr Tydvil Intermediate School. In 1925 he entered the University College of Wales, Aberystwyth, as a student in the Teacher's Training Department and graduated B.Sc. in 1928 with Second Class Honours in Chemistry. After completing the Diploma in Education, he pursued a course of research under the direction of Mr. C. R. Bury and was awarded the Ph.D. degree in 1931. Their work is published as a series of papers in the *Journal*.

Subsequently Davies was appointed Assistant-Lecturer in the Department of Chemistry at his College, where he proved to be a very capable teacher and research worker. Becoming interested in the study and teaching of micro-analytical methods, he assisted in the foundation of the Microchemical Club. In 1934 he became an officer in the College contingent of the Officers' Training Corps and in 1936 succeeded to the command. At the outbreak of war he organised and commanded the University of Wales (No. 2) Reception Unit at Cardiff and subsequently served with a training unit of the South Wales Borderers. He returned to Aberystwyth in 1940 to command the Senior Training Corps, in which he attained the rank of Major, and to resume his teaching work in the department of Chemistry. In carrying out these duties in the service of the associated University Colleges of London and Wales with efficiency and tact, he earned the commendation and gratitude of both institutions

T. Campbell James.

JOHN SIMPSON FORD.

1866—1944.

John Simpson Ford was born in Edinburgh in 1866 and died there on March 27th, 1944. He was educated at the Royal High School and University of Edinburgh. Before entering the latter, however, he had spent three years as an articled pupil of Falconer King, Public Analyst, during which time an inclination to take up medicine appears to have developed, for he went up to the University for that purpose. His success at Chemistry, however, led to his studying the subject under Professor Crum Brown, winning the Hope Prize in Chemistry.

In 1889 he was appointed chemist to Messrs. William Younger and Co., Ltd., and there he remained as chief chemist and afterwards as technical director until his death. A little time spent in Copenhagen under Jörgensen in 1893 led to an attempt by him to apply Hansen's single cell yeast technique to Scottish top fermentation brewing. The use of yeast grown from a single cell led to complications, as more than one

race or strain was needed to fulfil all the requirements of the Scottish brewing process. The fundamental problem arose as to whether greater importance should be attached to the selection of a race of top yeast or to the influence of environment on the selected race. In this case the chief factor in the environment was the chemical composition of wort. Ford's predilections were those of the chemist and he rightly considered on the evidence of his work that the environmental factors predominated.

In the early years of the century Ford was responsible for a number of papers on analytical methods, malt, Lintner soluble starch, etc., which appeared in the *Journals* of the Society of Chemical Industry, the Chemical Society, and the Institute of Brewing. But his best work was on malt diastase, and was mainly concerned with the influence of hydrogen and hydroxyl ions on the rate of action of the enzyme, and the stabilising effects on asparagin and phosphates—now recognised as pH buffers. It is clear that Ford was thinking in terms of hydrogen-ion concentration and buffer substances, although the convenient formulation of the pH scale by Sörensen and the widespread adoption of these ideas was not to take place for some years. Probably his best paper was the one with J. M. Guthrie read to the Institute of Brewing under the title " Contributions to the Biochemistry of Barley " (1908). In it evidence was furnished that the amylase of resting barley is largely inactive, probably bound to protein. This notion of a stock of enzyme formed during ripening and " fixed " in a stable inactive form in the resting corn, from which it could be liberated or activated when required, contributed usefully to the concept of a zymogen which was at that time being developed by Bayliss and others in respect of enzymes of the digestive tract. Even within recent years experimental work leading to mutually antagonistic hypotheses has been performed on the amylases of grain by Chrzaszcz and Myrbäck. From it one can conclude that the accuracy of Ford and Guthrie's experimental work and the soundness of their deductions remain fully established in the light of modern work.

During the first world war Ford served as a Lieutenant in the R.A.S.C., and in 1921 became a technical director to his firm. With the exception of papers (with Tait) on the determination of antiseptic value of hops and (with Fletcher) on brewing trials with new hybrid varieties of hops, Ford's later contributions to science and technology appear in the form of very many papers inspired by him but contributed by members of his staff, particularly Tait and Fletcher, to the *Journal* of the Institute of Brewing. However, a final paper from Ford appeared in 1941 on the occasion of the presentation to him of the " Horace Brown Medal " by the Institute of Brewing. Of necessity much of his work was not published.

Ford was possessed of the spirit of the investigator. He relied only on experimental evidence and sought it whenever possible. In drawing conclusions to his observations he always remained fully alive to alternative hypotheses.

He was a Fellow of the Chemical Society, the Institute of Chemistry, Royal Society of Edinburgh, original member of the Biochemical Society, for three years Chairman and honorary director of the Institute of Brewing's research.

His chief hobbies and recreations were motoring, photography, gardening, and, in early life, cycle racing, at which he won many medals. He was an indefatigable worker and a great source of inspiration and encouragement to his staff.

R. H. Hopkins.

FRANK LEE PYMAN.

1882—1944.

Frank Lee Pyman died on January 1st, 1944, in his sixty-second year. The traits of character that made his contributions to organic chemistry and to chemotherapy important were his persistence in the experimental attack of a problem from varied avenues of approach and his insistence that all observed facts must be accounted for by reasoning. Moreover, he always seemed to carry with him a great store of energy ready to be disseminated in endeavouring to reach the truth relating to any problem that interested him and he was able to think with lightning speed.

As a teacher and in the directing of research, the successes he achieved are to be attributed largely to these qualities combined with insistence on a high standard and businesslike ways and habits. His influence was augmented by the purposeful ends to which his researches were directed, for whether in the unravelling of chemical structure or in the extension of fundamental knowledge of organic reactions, his choice always lay in the direction of those researches which might directly or indirectly lead to the discovery of useful substances, especially in the field of medicine.

Pyman's grandfather, George Pyman, of Raithwaite Hall, Whitby, was a self-made man from the sea who eventually became the owner of a fleet of merchant vessels and in due course started shipping firms for his sons in several ports. George Pyman did much public work, becoming J.P. for Durham County, Councillor for the North Riding and Mayor of Hartlepool, and did much to develop the merchant shipping industry of Great Britain. Pyman's father, the fifth son of George, was a classicist who took honours at Cambridge—Trinity College—and subsequently read for the Bar, but abandoned this career in favour of a shipping business and a career in politics, at which he worked so hard that his health gave way in 1887. He acted as private secretary to Lord Rosebery; in 1892 he stood as candidate for Whitby in the Liberal interest. The disappointment of defeat caused a final break in his health, so that Frank Lee Pyman, then ten years of age, saw little of

his father thereafter. On his mother's side Pyman also inherited invaluable characteristics. His maternal grandfather, Henry Lee, who was at one time M.P. for Southampton, was head of the cotton firm Tootal, Broadhurst, and Lee. His daughter, Florence Lee, was Pyman's mother and on her fell the responsibility for the education of the family of six, of whom Frank Lee was the eldest, for her husband's illness developed into life-long disability. She was an exemplary mother, and Frank was ever ready to acknowledge his indebtedness for her influence during childhood and her advice in later life.

Pyman was born on April 8th, 1882, and received his schooling at Dover College. There he took a great liking to chemistry : his teacher, Pendlebury, encouraged him in adopting this as his career. At seventeen he went to Owens College, Manchester, gaining a James Gaskell Scholarship. There he came under the influence of W. H. Perkin, junior. Thus his inborn ability for practical science became directed to organic chemistry, in which he was later to achieve so much.

That he was an exceptional student is clear from the following account written by one of his contemporaries. " He was of a different class from most of us. We could see his ability from the first year and as time went on we realised that he was brilliant and an outstanding man, for on top of his ability to understand things more quickly than the rest of us, he was the hardest worker of the whole year.

" I think I have never seen a neater worker anywhere. His organic preparations were not made in large (and useless) quantities, but in test tubes. Everything was in apple-pie order on his desk, his note-book somehow escaped the stains and burnings which seemed the lot of us lesser men.

" And yet he was not a man aloof but a good mixer and a man whose company I always enjoyed. If I was in difficulties over some point I could not understand, Frank was always willing to help and explain most patiently. His unbounded enthusiasm for everything he took up was infectious. There seemed nothing he could not do and yet we never felt he despised us, nor did jealousy for his powers ever trouble us. If any rag was proposed, Frank would be in the thick of things."

These qualities of friendship continued with little change throughout his life and his rather breezy, frank and open way with his friends which was the basis of it was equally helpful to those who worked and those who played with him.

After graduating with first-class honours in 1902, he went to Zurich Polytechnic to study under Bamberger, with whom he engaged in research for which he was awarded a Ph.D. in 1904.

On his return to this country he spent a short period under T. E. Thorpe in the Government Laboratory. There he became dissatisfied through not finding opportunity to carry on research in organic chemistry, of which he had become enamoured and in 1906 he was appointed on the staff of Experimental Laboratories of the Wellcome Chemical Works, Dartford, and soon succeeded H. A. D. Jowett as head of the Department. During the next thirteen years he was engaged in research work on behalf of Burroughs Wellcome & Co., later succeeding F. B. Power as head of the Wellcome Research Laboratories in London. Thus he became interested in the application of chemistry to progress in therapeutics, to which the greater part of his experimental work was later devoted.

In 1919 he was appointed Professor of Technological Chemistry in the University of Manchester and in the Manchester College of Technology and for the next eight years he took a very active part in the academic life of Manchester.

At the College of Technology Pyman inherited a large staff, for the most part senior to him in age, length of service and technical knowledge, and with remarkable rapidity he succeeded in establishing the right influence and atmosphere to enable him to obtain for the University the best possible service from each of them. Professor F. M. Rowe, who at this time became his colleague, says of him : " It was Pyman's keenness for research and his ability for experimental work with his own hands, his desire to see all theoretical laboratory teaching at the highest possible standard and, above all, his businesslike ways which enabled him to knit his staff together so effectively. He had no use for a slacker, but once he was satisfied with the competence of a particular member of his staff, then he left that man very much to his own devices subsequently, although he was always available and ready to help if consulted.

" Pyman soon had a small laboratory equipped next to his private room and in it he settled down to his own work on glyoxaline derivatives, there being in it also space for one or two of the best graduates who elected to work under him on this subject. Pyman became extremely popular with all his really first-class students, but less so with the less well-prepared ones, who were not really ready, without further training, to succeed with preparative work in the glyoxaline series."

When the Fellowship of the Royal Society was conferred upon him in 1922 the students of the College insisted on forming a procession and taking him through the streets of Manchester in celebration.

In the year 1927 Pyman relinquished his Professorship in Manchester University in order to become Director of Research at the Nottingham Laboratories of Boots Pure Drug Co., the position he continued to hold until his death in 1944. There he gathered round him a group of research workers suited to his leadership; the department grew rapidly and a period of great activity followed.

Apart from publications made during the sixteen years which followed, Pyman was able to make substantial contributions to the development of manufacturing processes relating to arsphenamine, insulin, liver extract, saccharin and potassium permanganate.

In 1929 he was appointed a Director of Boots Pure Drug Company and took part in discussions on general commercial and industrial affairs. He was characteristically diffident about expressing an opinion if he felt

his knowledge did not justify him or if he considered the problem to be unsuitable for solution by the scientific method of approach. His gift of clear and concise expression inspired confidence and enabled him to put his views with great force.

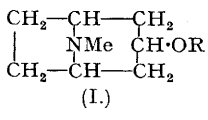
Pyman inaugurated regular monthly research conferences between selected academic workers in Chemistry, Biochemistry and Medicine and his scientific colleagues of Boots Pure Drug Co. He acted as chairman of this conference and thus most successfully assisted in the building of that bridge of understanding between academic and applied science for which so great a need exists.

In 1907 Pyman was married to Ida Catrine Lowry, daughter of George Lowry, and throughout the years that followed, in indirect ways she contributed greatly to his successful achievements. Pyman's home life was an especially happy one. The day's work finished and at week ends, he wanted nothing more than to be at home with his wife and family. One remembers how lustily he played with his children when they were young and how his interest in them in later life took precedence of everything else.

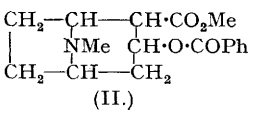
He played golf and billiards, but his chief recreation was that of gardening, at which he worked with great zeal. Moreover, his interest in horticultural science extended beyond his own garden, for the directing of Boots horticultural research became one of his many activities in later years. He paid many visits to other countries and these gave him and his wife great pleasure. They were both lovers of music and one of the few things that would draw him away from home was attendance at the opera, particularly when abroad. He also took great interest in orchestral gramophone music, Beethoven being his first choice.

Pyman's papers cover a considerable diversity of topics—essential oils, glucosides, alkaloids, glycerophosphates, organic compounds of arsenic, selenium amd bismuth, etc., but his work can be discussed as a contribution to three main subjects, which evoked his special interest.

His first paper, published with Jowett, started a series on the relation between chemical constitution and physiological action, which continued throughout his career. Jowett and Pyman began with a study of the tropeines (I), which are acyl esters of the amino-alcohol, tropine, the best known members of the group being the natural alkaloids, hyoscyamine and atropine, the *l*- and the *dl*-tropyl ester respectively. The useful tropeines are mydriatics, and as the effect of this action is readily observable in a roughly quantitative fashion, it was used to investigate the results of varying the acyl radical as indicated by R in (I).



(I.)



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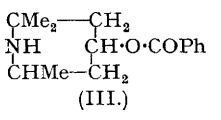

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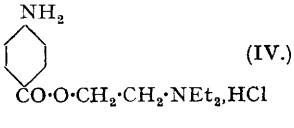


(IV.)

From this study Jowett and Pyman (J., 1909, **95**, 1020) were able to draw the following conclusions :— The current generalisation that a tropeine to have mydriatic properties must have (1) a benzene nucleus and (2) an aliphatic hydroxyl in the side chain containing the carboxyl group is not valid. The first postulate is approximately correct, but benzene may sometimes be replaced by pyridine, as in the moderately active β-2-pyridyl-α-hydroxypropionyltropeine. The second postulate is incorrect and cases were found in which the hydroxyl group was nuclear, absent, replaced, or closed by lactone formation, without disappearance of mydriatic activity. It is valid to the extent that all the new tropeines tried and found at least as potent as homatropine, contained an alcoholic hydroxyl group.

From the tropeines it was a natural step to deal with local anæsthetics, since ecgonine, the basic nucleus of cocaine (II), is a tropinecarboxylic acid and tropacocaine, also a potent local anæsthetic, is the benzoic ester of *ψ*-tropine. Though cocaine is probably still the best all-round local anæsthetic, it has for many purposes been replaced by substitutes, which resemble it in being benzoyl esters of amino-alcohols. The skeleton $:\dot{N}\cdot\dot{C}\cdot\dot{C}\cdot O\cdot COR$ is common to most of the well-known local anæsthetics, *e.g.*, cocaine (II), β-eucaine (III), and novocaine (IV). Pyman prepared a series of compounds (V to IX) based on this skeleton (J., 1908, **93**, 1793) and a second series (X to XIII) of a more exploratory character (J., 1917, **91**, 167). Compounds (V) to (IX) all showed local anæsthetic activity, indicating that this skeletal structure has some influence in producing this property, but they were too toxic and irritant on injection to be of practical value. The second series (X to XIII) provided some striking contrasts. It was known that replacement of benzoyl by phenylacetyl in cocaine (II) led to loss of activity, whereas a similar change in α-eucaine has been stated to enhance the action. In this second series ethyl *p*-aminophenylacetate (X) proved inactive in contrast with ethyl *p*-aminobenzoate.

(V.) $Ph\cdot CO\cdot O[CH_2]_2\cdot NR\cdot[CH_2]_2\cdot O\cdot COPh$. R = Me, inactive : R = Et, just active.

(VI.) $Ph\cdot CO\cdot O\cdot CH(CH_2R)\cdot CH_2\cdot O\cdot COPh$. R = NMe_2, NEt_2 or $C_5H_{10}N$, active.

(VII.) $C_5H_{10}N\cdot CH_2\cdot CH_2\cdot O\cdot COPh$. Slightly active.

(VIII.) $Ph\cdot CO\cdot O\cdot[CH_2]_2\cdot N\langle{}^{CH_2\cdot CH_2}_{CH_2\cdot CH_2}\rangle N\cdot[CH_2]_2\cdot O\cdot COPh$. Active.

(IX.) $NMe_2\cdot CH_2\cdot CHR\cdot O\cdot COPh$. R = piperonyl, active.

(X.) $p\text{-}NH_2\cdot C_6H_4\cdot CH_2\cdot CO_2Et$. Inactive.

(XI.) $p\text{-}NH_2\cdot C_6H_4\cdot CH_2\cdot CO\cdot O\cdot CH_2\cdot CH_2\cdot NEt_2$. Inactive.

(XII.) $NEt_2\cdot CH_2\cdot CH(OR)\cdot CH_2\cdot OPh$. R = H, active : R = COPh, too acid for test.

(XIII.) $p\text{-}NH_2\cdot C_6H_4\cdot CO\cdot NH\cdot C_6H_4\cdot OEt\text{-}p$. Inactive.

Similarly (XI), which is " novocaine " (IV) with its *p*-aminobenzoic acid group replaced by a *p*-aminophenylacetic residue, is inactive. In (XII) it was hoped to test the effect of replacing one benzoyl group of (VI) by a phenyl group. The benzoate (XII, R = COPh) was too acid for test, but the alcohol (XII, R = H) was active.

The dystherapeutic effect of a slight change in the acyl radical in these local anæsthetics is in strong contrast to the behaviour of the tropeines, where, as Jowett and Pyman found, the tropyl group may be replaced by acids ranging from phenylacetyl to phthalidecarboxyl and β-2-pyridyl-α-hydroxypropionyl without disappearance of mydriatic activity.

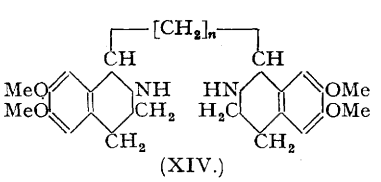
At this period there was a disposition on the part of chemists to believe that similarity in chemical structure implied similarity in pharmacological action. It is now known that, though this simple relation between chemical structure and pharmacological action may be shown over a limited range, *e.g.*, in a homologous series of compounds, it is not generally valid and other factors, physical and biological, are at least as important as the molecular architecture. Pyman's early work on this subject contributed materially to realisation of the complexity of the factors involved in attempts to synthesise substances having a required pharmacological action and his later papers illustrate the development of these ideas. Thus, in his paper (with E. C. S. Jones; J., 1925, **127**, 2588) on pungency in acid amides of the capsaicin (decenovanillylamide) type, he states, amid conclusions relating to variation in structure, that the shape of the side chain, rather than its weight, determines the degree of pungency.

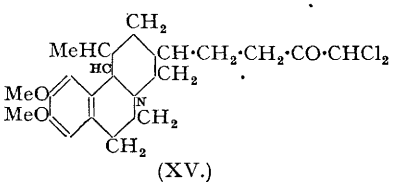
The paper on " The Variation of Phenol Coefficients in Homologous Series of Phenols " (with C. E. Coulthard and J. Marshall; J., 1930, 280) involves biological conditions of a simple type and, as might be expected, the results are free from the kind of contrast referred to above. Using the series of alkyl side chains from methyl to *n*-heptyl in phenol, the three cresols and guaiacol, it is shown that in each series the phenol coefficient rises to a maximum at the *n*-amyl derivative, and then falls, the highest figure being given by 5-*n*-amyl-*o*-cresol. Mention must also be made of the work on amidines of pharmacological interest (with A. P. T. Easson; J., 1931, 2991), in which stress is laid on the structural similarity of the amidine group, $\cdot C(:NH)\cdot NH_2$, to the carboxyl group and to the solubility of amidine bases in both water and immiscible solvents. On these grounds it was considered worth while to try replacement of the carbethoxy-group by the amidine group for local anæsthetic action. *p*-Aminobenzamidine was inactive as compared with ethyl *p*-aminobenzoate, but *p*-carbethoxybenzamidine, $CO_2Et\cdot C_6H_4\cdot C(:NH)\cdot NH_2$, was slightly active and benzenylveratrylamidine, $NH_2\cdot CPh:N\cdot C_6H_3(OMe)_2$, showed well-marked activity.

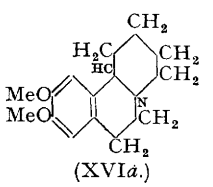
Various amidines were also tried biologically in other directions; they were weak antiseptics, had no well-defined action as hypoglycæmic drugs and were inactive in canary malaria, but one at least, *p*-hydroxyphenylacetamidine, $HO\cdot C_6H_4\cdot CH_2\cdot C(:NH)\cdot NH_2$, like its relative *p*-hydroxyphenylethylamine, showed pressor action, which disappeared in its *N*-methyl derivative.

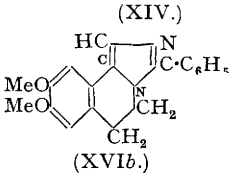
Probably the most interesting of all Pyman's contributions to this subject was described in his presidential address to the chemical section of the British Association in 1937 (*J. Soc. Chem. Ind.*, 1937, **56**, 789). It arose out of his important work on emetine, which is referred to later. Emetine is used in medicine as a remedy for amœbic dysentery and in the hope of finding a synthetic substitute he devised a method of preparing substances of the type represented by (XIV; cf. emetine). Six of these products were made (Child and Pyman, J., 1929, 2010) and tested as amœbicides and anti-malarials and found inactive. Attention was next directed (Child and Pyman, J., 1931, 36) to a series suggested by the amœbicidal activity (Pyman and Wenyon, *J. Pharm. Exp. Ther.*, 1917, **10**, 237) of a substance, $C_{20}H_{27}O_3NCl_2$, derived from cephaeline and for which Brindley and Pyman (J., 1927, 1067) had proposed formula (XV), which retains the reduced benzpyridocoline nucleus of the emetine formula (XXXII). Typical examples of the compounds synthesised are (XVI*a*) and (XVI*b*). Of the eight substances tested, the most active was (XVI*b*), which inhibited the growth of *Entamœba histolytica* in cultures at 1 in 25,000 compared with emetine, which was effective at 1 in 500,000.

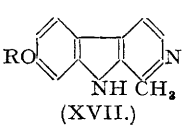
Attention was next given to the alkaloids harmine and harmaline, which had acquired an undeserved reputation as anti-malarials. These were demethylated and from the resulting phenolic bases, harmol and harmalol, homologous series of alkyl ethers (XVII; harmol ethers, R = alkyl) were prepared and submitted to biological tests. They were inactive in bird malaria, and were not trypanocidal, but there was a peak of anti-bacterial activity at *O*-*n*-butylharmol for *B. typhosus* and at *O*-*n*-amylharmol for *Staphylococcus aureus*.

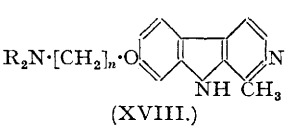

(XIV.)


(XV.)


(XVI*a*.)


(XVI*b*.)

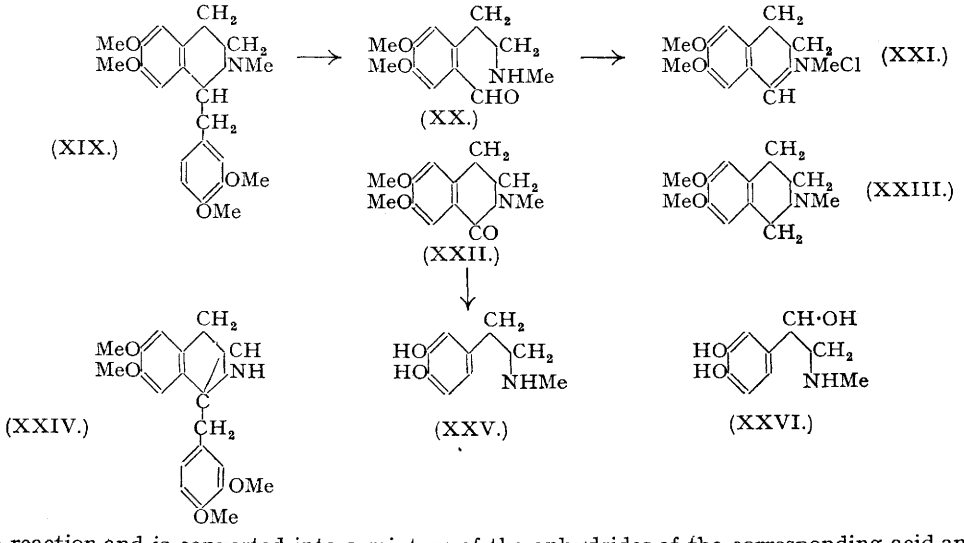

(XVII.)


(XVIII.)

Maximum amœbicidal activity was reached at *O*-*n*-nonylharmol for the alkyl ethers (with Coulthard and Levene, *Biochem. J.*, 1933, **27**, 727; cf. Coulthard, *ibid.*, 1934, **28**, 264), but as this substance had the undesirable property of yielding sparingly soluble salts, a solubilising component was introduced in place of a simple alkyl group and a new homologous series of compounds represented by (XVIII) was made, the size of R (the *N*-alkyl group) and of *n* being varied. In this series the peak of amœbicidal activity was reached at *Q*-λ-di-*n*-butylaminoundecylharmol (1 in 750,000 to 1 in 4,000,000) compared with *O*-*n*-nonylharmol at (1 in 200,000 to 1 in 500,000) and emetine (1 in 2,000,000 to 1 in 10,000,000). These results indicated that in the development of amœbicidal action in this series the side chain was more important than the harmol nucleus. Preliminary experiments showed that the attachment of the chain $(C_4H_9)_2N\cdot[CH_2]_{10}\cdot$ to a simple substituted amino-group seemed to give high amœbicidal efficiency. A series of substances of the type $NRR'\cdot[CH_2]_n\cdot NRR'$ was prepared and trials of this group of compounds indicated a peak of activity (1 in 3,000,000) at ακ-tetra-*n*-amyldiaminodecane and no variants on this gave higher efficiency.

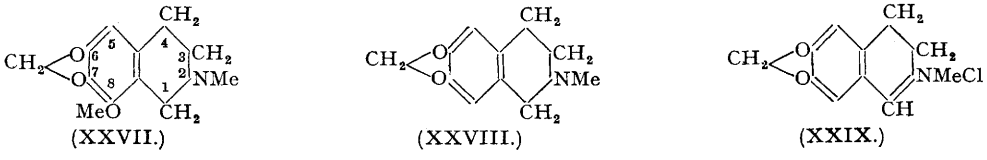
iso*Quinoline Alkaloids*.—In 1909 Pyman showed that, just as narcotine and hydrastine undergo hydrolytic oxidation to cotarnine and hydrastinine respectively, so laudanosine (XIX; *N*-methyl-1 : 2 : 3 : 4-tetrahydropapaverine) can be converted into 4 : 5-dimethoxy-2-β-methylaminoethylbenzaldehyde (XX) (J., 1909, **95**, 1266), which in the form of its salt, 6 : 7-dimethoxy-2-methyl-3 : 4-dihydro*iso*quinolinium chloride (XXI), came into medical use as a uterine styptic.

Extension of this investigation to other substituted tetrahydro*iso*quinolines led to the conclusion that, whereas 1-alkyl derivatives do not react in this way, 1-benzyl, 1-benzyl-2-alkyl and 1-benzyl-2-acyl derivatives can undergo this simultaneous oxidation and scission (J., 1909, **95**, 1738). This investigation included work [*ibid.*, p. 1610; (with Reynolds), J., 1910, **97**, 1320; 1915, **107**, 176] on the reduction products of papaverine. Pyman cleared up the existing confusion and found that in addition to tetrahydropapaverine, there was formed an anomalous product, pavine, at first believed to be 1 : 2-dihydropapaverine, but which was eventually shown by a study of its exhaustive methylation products to have a bridged-ring structure as in (XXIV). When 6 : 7-dimethoxy-2-methyl-3 : 4-dihydro*iso*quinolinium chloride (XXI) is boiled with alkali, it undergoes a



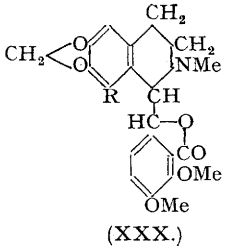
Cannizzaro reaction and is converted into a mixture of the anhydrides of the corresponding acid and alcohol, *viz.*, 1-keto-6 : 7-dimethoxy-2-methyltetrahydro*iso*quinoline (XXII) and 6 : 7-dimethoxy-2-methyltetrahydro*iso*quinoline (XXIII). The former can be hydrolysed, undergoing demethylation of both methoxyl groups and hydration of the lactam group, yielding 3 : 4-dihydroxyphenylethylmethylamine (XXV) a substance qualitatively resembling adrenaline (XXVI) in pharmacological action (J., 1910, **97**, 264).

Continuing work on *iso*quinoline alkaloids, Pyman and Remfry (J., 1912, **101**, 1595) accomplished the conversion of cotarnine into hydrastinine. The former was reduced to hydrocotarnine (XXVII), and the methoxyl group of the latter eliminated by the action of sodium in fusel oil to yield hydrohydrastinine (XXVIII), which was oxidised to hydrastinine (XXIX; as chloride). In this reaction four interesting phenolic bases are also formed in small quantity by the following replacements : CH_2O_2: at 6 and 7 into OH at 6 or 7 and H at 7 or 6, with or without the substitution of H at 8 for MeO (see XXVII). Up to that time, hydrastinine had been made from the costly alkaloid hydrastine and this new procedure made the relatively cheap opium alkaloid, narcotine, available as the primary material.

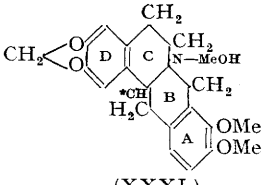


In 1931 Pyman was associated with Hope, Remfry, and Robinson (J., 1931, 236) in a synthesis of hydrastine (XXX, R = H) which had features of special interest. This alkaloid has two asymmetric carbon atoms and two *dl*-forms (*a*) and (*b*) were obtained. In a subsequent paper (J., 1934, 1315) dealing with the stereoisomerides of narcotine (XXX, R = OMe) and hydrastine (XXX, R = H) it was shown that the natural forms, *l*-narcotine and *l*-hydrastine, are each converted by hot methyl-alcoholic potassium hydroxide into a mixture of the original alkaloid and a new, optically active isomeride, due to partial racemisation at one asymmetric carbon atom, presumably that of the " phthalide " nucleus. In the case of narcotine, the new isomeride, *l*-β-narcotine, is of lower lævorotation than natural, *l*-α-narcotine, whilst in the case of hydrastine the new form is of higher lævorotation. Hydrastine is therefore considered to differ from natural narcotine in stereochemical configuration and to be *l*-β-hydrastine, the new form being *l*-α-hydrastine. On this basis the complete synthesis of the natural form of hydrastine will probably involve the resolution of hydrastine-*b*, which should yield *l*-α-hydrastine, and it was shown that the latter can be epimerised in minute amount by hot methyl-alcoholic potassium hydroxide.

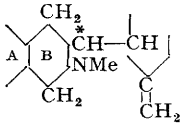
Pyman's work on berberine and its derivatives began with an account of the oxidation of berberine-acetone to the phenol-betaine *neo*oxyberberine (J., 1911, **99**, 1690). Somewhat later he investigated with Jowett (J., 1913, **103**, 290) the bark of *Xanthoxylum brachyacanthum*, F. Muell., and showed that it contained γ-homochelidonine in small amount, and in much larger proportion a second alkaloid, which was isolated in the form of its chloride and shown to be *l*-α-tetrahydroberberine (canadine) methochloride (XXXI with OH → Cl). This led to a study (J., 1913, **103**, 817) of the two forms, α- and β-, of the methochloride.



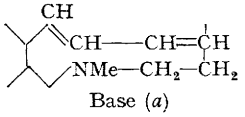
(XXX.)



(XXXI.)



Base (*b*) = *dl*-form
Base (*c*) = *l*-form



Base (*a*)

Both caused paralysis of voluntary muscle, similar to that produced by curare, but the two provided another instance of the influence of configuration on pharmacological action, the α-form being only one-tenth as active as the β-form. Out of this work arose the completion (J., 1913, **103**, 817) of the work done by Voss and Gadamer (*Arch. Pharm.*, 1910, **248**, 43; cf. McDavid, Perkin, and Robinson, J., 1912, **101**, 1218) in explaining the reactions occurring when the tetrahydroberberine alkylhydroxides are heated. Pyman showed that three anhydro-bases can be formed and that their relative proportions depend on the experimental conditions and on the configuration of the starting material. Thus he found that while the *dl*-form of tetrahydroberberine methohydroxide (XXXI) gave rise to two anhydro-bases (*a*) and (*b*), the *l*-form gave an optically active form (*c*) in addition to (*a*) and (*b*), the yield of base (*a*) being the same in both cases, while that of (*b*) in the first case is about equal to that of (*b*) + (*c*) from the *l*-form, indicating that (*b*) is the racemic form of (*c*). Under certain experimental conditions, base (*a*) is not found in the reaction products, owing to the fact that it is unstable under these conditions and is converted into the *dl*-methohydroxide (XXXI), which then yields the *dl*-anhydro-base (*b*). The course of the reactions was represented thus :

l-Canadine methohydroxide ⟶ Base (*a*) ⇄ *dl*-Tetrahydroberberine methohydroxide

↓ ↓

Base (*c*) Base (*b*)

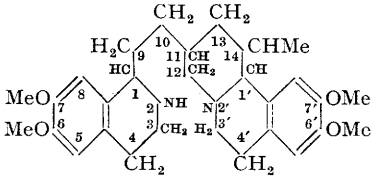
The culminating point in Pyman's work on *iso*quinoline alkaloids is that on the ipecacuanha bases, which was begun with Carr (J., 1914, **105**, 1591) in order to clarify the then somewhat confused chemistry of this drug, which just previously had been successfully used in cases of amœbic dysentery. The work was continued by Pyman until 1927 [J., 1917, **111**, 419; 1918, **113**, 222; (with Brindley), J., 1927, 1067]. The three known ipecacuanha alkaloids, emetine, cephaeline and psychotrine, were first prepared, carefully purified and characterised, new empirical formulæ assigned to them, and their inter-relationships established. For the first time, clear evidence that they belonged to the *iso*quinoline group of alkaloids was provided by the isolation of 6 : 7-dimethoxy*iso*quinoline-1-carboxylic acid from the oxidation of emetine by permanganate. In 1917 two new alkaloids were isolated from the drug, of which one, emetamine, could not at once be related to any of the three already known. The second proved to be psychotrine methyl ether and the following interconversions were effected :

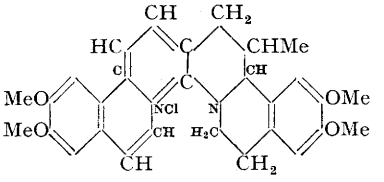
Cephaeline	←	Psychotrine	⟶	*iso*Cephaeline
$C_{25}H_{28}N_2(OMe)_3OH$		$C_{25}H_{26}N_2(OMe)_3OH$		$C_{25}H_{28}N_2(OMe)_3OH$
↓		↓		↓
Emetine	←	*O*-Methylpsychotrine	⟶	*iso*Emetine
$C_{25}H_{28}N_2(OMe)_4$		$C_{25}H_{26}N_2(OMe)_4$		$C_{25}H_{28}N_2(OMe)_4$

Some progress had also been made with the Hofmann degradation of emetine and in the determination of characteristics bearing on the constitution of all five alkaloids.

In 1927, Späth and Leithe provided evidence of the existence of a second *iso*quinoline nucleus in emetine and, on that basis, suggested a partial formula for this alkaloid. This led Pyman to publish a formula for emetine, which Sir Robert Robinson had suggested two years previously, based on a theory of structural or genetic relationships among the *iso*quinoline alkaloids. This formula was modified slightly by the transfer of a methyl group from C_{12} to C_{14} (XXXII), mainly to account for the oxidation of emetine, *iso*emetine or *O*-methylpsychotrine to the deep-red substance, rubremetinium chloride (XXXIII), in the formation of which eight hydrogen atoms are lost from emetine and one of the nitrogen atoms becomes quaternary, while the other ceases to show basic properties assumed to be due to amidine formation. Formulæ, based on that of emetine, were also suggested for the other ipecacuanha alkaloids.

(XXXII.)





(XXXIII.)

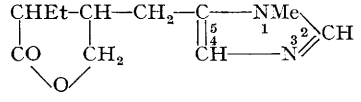
Mention has been made already of the work on synthetic amœbicidal drugs, suggested by this investigation of emetine and its associates.

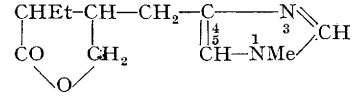
Other Alkaloids.—Pyman also published a number of papers on other alkaloids, notably conessine and holarrhenine (J., 1919, **115**, 163) derived from *Holarrhena congolensis*, a drug which was alleged to exert a local anæsthetic action and is still of some interest as a not very satisfactory remedy for amœbic dysentery. He also isolated and characterised a series of three alkaloids from the Australian plant *Daphnandra micrantha* (J., 1914, **105**, 1679).

Most of the *Datura* species examined up to 1908 had been found to contain one or more of the usual solanaceous alkaloids, atropine, hyoscyamine or hyoscine and Pyman and Reynolds (J., 1908, **93**, 2077) in their discovery of meteloidine in *Datura meteloides* found a solanaceous alkaloid of a new type, in which the basic nucleus tropine was replaced by teloidine, which King (J., 1919, **115**, 487) has suggested is probably a trihydroxytropane, and the typical esterifying acid, tropic or benzoic, was replaced by tiglic acid.

Pilocarpine and Glyoxaline.—The subject which probably interested Pyman more than any other, *viz.*, the chemistry of glyoxaline, also arose primarily from an alkaloidal investigation. In the years 1900 to 1903, thanks to the work of Jowett in this country and Pinner in Germany, Pinner and Schwarz were able to suggest a formula (XXXIV) for pilocarpine. Jowett confirmed this suggestion by the isolation of a series of dialkylglyoxalines from the products of distillation with soda-lime of *iso*pilocarpine, a stereoisomeride of pilocarpine, though he pointed out that these dialkylglyoxalines might be either 1 : 4- or 1 : 5-dialkyl derivatives, and that consequently pilocarpine was as likely to be represented by (XXXV) as by (XXXIV).

(XXXIV.)

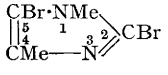


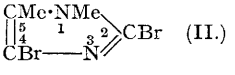


(XXXV.)

That the 1 : 5-formula (XXXIV) was probably correct was indicated by Pyman (J., 1910, **97**, 1814) from a study of the two dimethylglyoxalines produced by the methylation of 4 (or 5)-methylglyoxaline. The latter, like all glyoxalines containing a free imino-hydrogen atom, shows virtual tautomerism between positions 4 and 5, whence the two dimethylglyoxalines must be the 1 : 4- and 1 : 5-forms. The one having b. p. 224—225° was identical with the substance obtained from *iso*pilocarpine. Both yielded dibromo-compounds, which must be represented thus :

(I.)

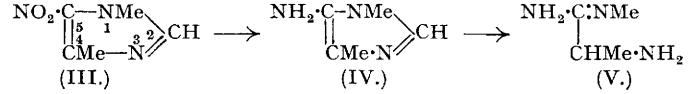




(II.)

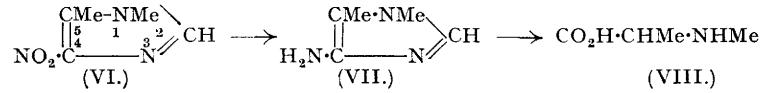
Pyman found by a simple distribution method that one of these dibromo-compounds was a weaker base than the other, which he explained as due to the proximity of the bromine atoms at C_2 and C_4 to the basic N at position 3 as in (II) and since the weaker base is the derivative of the dimethylglyoxaline from *iso*pilocarpine, it was assumed that the latter, and therefore pilocarpine also, yielded 1 : 5-dimethylglyoxaline. This assumption was proved correct in Pyman's later work on the reduction of the nitro-derivatives of the two dimethylglyoxalines (J., 1922, **121**, 2616), the results of which may be represented thus :

A.



(III.) (IV.) (V.)

B.

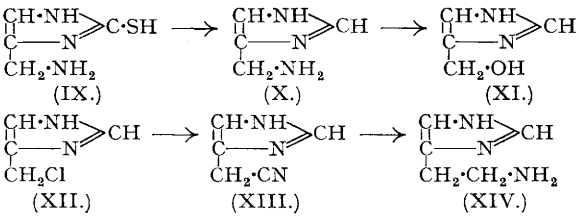


(VI.) (VII.) (VIII.)

The identity of (V) as *dl*-alanine-*N*-methylamidine was established by its hydrolysis to *dl*-alanine, ammonia and methylamine, which also accompany it in the primary reaction. Similarly *dl*-*N*-methylalanine (VIII) in operation B is accompanied by ammonia.

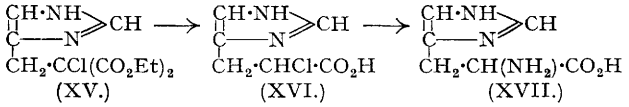
Pyman also added the new alkaloid pilosine to the jaborandi series (J., 1912, **101**, 2261). It is decomposed by boiling with alkali into benzaldehyde and a new alkaloid, pilosinine, which closely resembles pilocarpine and *iso*pilocarpine in physical and chemical properties and in pharmacological action, and is regarded as a lower homologue of this pair, corresponding stereochemically with *iso*pilocarpine. The parent alkaloid pilosine is represented by the formula for pilocarpine (XXXIV) with the ethyl group replaced by $C_6H_5{\cdot}CH{\cdot}OH$.

While this orientation of substituents in the glyoxaline nucleus was proceeding, another natural product with the same nucleus began to attract interest, *viz.*, histamine (4-β-aminoethylglyoxaline), a substance with potent pharmacological action, whose occurrence in ergot extracts had been discovered by Barger and Dale (J., 1910, **97**, 2592). Its preparation from histidine was improved (with Ewins, J., 1911, **99**, 339) and processes for the synthesis of it and a number of its homologues devised (J., 1911, **99**, 668, 2172; with Fargher, J., 1921, **119**, 734; with Garforth, J., 1935, 489), of which the first may be mentioned. 2-Thiol-4-aminomethylglyoxaline (IX) on oxidation by nitric acid yielded, instead of the expected aminomethylglyoxaline (X), 4-hydroxymethylglyoxaline (XI). The hydroxyl group in the latter was replaced by chlorine, and the 4-chloromethylglyoxaline (XII) treated with potassium cyanide to give 4-cyanomethylglyoxaline (XIII), which was then reduced by sodium in alcohol to the required base, 4-β-aminoethylglyoxaline (XIV).



(IX.) (X.) (XI.) (XII.) (XIII.) (XIV.)

4-Chloromethylglyoxaline (XII) proved to be a reactive substance and Pyman was able to use it to synthesise substances structurally allied to pilocarpine (J., 1912, **101**, 530) and for his well-known synthesis of histidine (J., 1911, **99**, 1386). For the latter purpose it was condensed with ethyl sodiochloromalonate to give ethyl 4-glyoxalinemethylchloromalonate (XV), which was hydrolysed and partially decarboxylated to *dl*-α-chloro-β-glyoxaline-4-propionic acid (XVI). This, when heated with concentrated aqueous ammonia at 110°, yielded *dl*-histidine (XVII), which was resolved by fractional crystallisation of the acid tartrate to yield *l*-histidine identical with the natural product.



(XV.) (XVI.) (XVII.)

A second synthesis starting from glyoxaline formaldehyde was published later (J., 1916, **109**, 186).

In 1919 Pyman began a more academic study of reaction and substitution in the glyoxaline nucleus and this was continued and developed after his professorial appointment at Manchester. It included particularly an investigation of the bromination of glyoxaline and the 1-, 2- and 4-methylglyoxalines (with Balaban, J., 1922, **121**, 947; 1924, **125**, 1564; Light, J., 1922, **121**, 2626; Timmis, J., 1923, **123**, 494), the direct sulphonation of glyoxaline, 2-methylglyoxaline, and its 4-bromo-derivative, and 4(5)-methylglyoxaline (with Ravald, J., 1920, **117**, 1429; Forsyth and Moore, J., 1924, **125**, 919; Barnes, J., 1927, 2711); the nitro- and related derivatives of glyoxaline and its alkyl and aryl compounds (with Fargher, J., 1919, **115**, 217, 1015; Grant, J., 1921, **119**, 1893; Stanley, J., 1924, **125**, 2484; Bhagwat, J , 1925, **127**, 1832; Forsyth and Numkar, J., 1926, 800, 2912 : 1930, 397; Bryans, J., 1929, 549) and probably most important of all, the series of seven papers on the tautomerism of amidines inspired, no doubt, by his successful solution of the pilocarpine alkyl orientation problem already referred to, and concerned first with alkylation in the nitro- and aryl-glyoxalines and eventually extended to the alkylation of open-chain amidines, arylamidines and pyrimidines (J., 1923, **123**, 361, 367, 3359; with Hazeldine and Winchester, J., 1924, **125**, 1431; Forsyth, J., 1925, **127**, 573; 1926, 2502; Chew, 1927, 2318).

The need for brevity imposed by present conditions makes it impossible to summarise the knowledge thus gained of the chemistry of this interesting and biologically important heterocyclic nucleus.

For the same reason the foregoing account has had to be restricted to the three principal types of investigation which interested Pyman. They at least serve to indicate the importance of his contribution to the progress of our science, which he served so devotedly throughout his life. Pyman will be remembered not only as a chemist of outstanding gifts but as a man upright in all he did and of unswerving loyalty to his friends and colleagues.

FRANCIS H. CARR.
T. A. HENRY.

GEORGE STALLARD.

1854—1944.

GEORGE STALLARD, who died on April 5th, 1944, was one of the oldest Fellows of the Chemical Society, having been elected in December, 1879. He was the *doyen* of Science Masters in public schools, having held appointments at St. Paul's and Rugby, where he organised the teaching of chemistry on modern lines with strong emphasis on laboratory work.

He was born on July 6th, 1854, the son of Mr. George Stallard of Havant, the owner of a parchment factory. He was educated at Hurstpierpoint College and proceeded with a scholarship to Keble College, Oxford, whence in 1876 he took an Honours Degree (first class) in Natural Science, with chemistry as his principal subject.

As there was no chemical teaching at Keble College, Stallard went for lectures and laboratory work to the University Chemical Department at the Museum. Odling was then the Professor, and W. W. Fisher and John Watts superintended the laboratory work. Stallard found Watts a well-informed and painstaking teacher and was fortunate in securing him as his private tutor. Stallard always acknowledged his great indebtedness to Watts.

After taking his degree, Stallard was appointed Science Master at the Bedford County School at Elstow, which had adopted a modern curriculum but where Stallard had to teach several subjects besides chemistry. From there in 1878 he went to St. Paul's, then in the City, as its first Science Master, although still having also to teach other subjects than chemistry. F. W. Walker was Headmaster and was not credited with much enthusiasm for science teaching. He began by giving Stallard the option of teaching some other subject than chemistry. Stallard preferred to adhere to chemical teaching and Walker, evidently impressed by his sincerity, afterwards gave him every encouragement, so that Stallard looked back on his five years at St. Paul's as the happiest time in his school life.

His first pupil was a new boy who desired to take up chemistry and who had not been changed by Walker's advocacy of other subjects. He came with the boy to Stallard's room and said, " I hand over this boy to your care, body and soul." That boy was my brother, the late Professor M. J. R. Dunstan, who from St. Paul's gained a Postmastership at Merton College, Oxford, took an Honours Degree in Chemistry, and became successively Principal of the Wye Agricultural College and the Cirencester Agricultural College.

On going to Rugby in 1883, Stallard found Jex-Blake as Headmaster and again in addition to chemistry was required to teach other subjects. There was then no proper laboratory. In 1887, Percival succeeded Jex-Blake. He came from Clifton, where Tilden had made great headway in the teaching of chemistry. Stallard was now able to devote himself entirely to chemistry and, although there was no adequate laboratory until 1905, he continued to make chemistry of increasing interest to the boys, with whom he had some conspicuous successes. Among these were Nevil Sidgwick, now Professor at Oxford, and Sir Will Spens, Vice-Chancellor and Master of Corpus Christi College, Cambridge.

Stallard soon acquired great influence in the school. In 1893 he became a House Master, built Tudor House, and firmly established chemistry in the school curriculum, largely owing to the improvements he made in laboratory teaching. He took immense trouble in teaching both the ordinary boys and those whom he was preparing for scholarship examinations. He retired in 1913.

In 1887, the British Association appointed a Committee to report on the teaching of chemistry in schools, of which Dr. W. J. Russell was chairman and I was secretary. Stallard was one of the members and with Francis Jones (Manchester), Dunn (Bath), and Shenstone (Clifton), took an active part in the proceedings.

Above all Stallard was a schoolmaster but with many other interests. He was interested in art, was well read in English literature, was a good linguist, was active in sport, and while at Rugby was often to be seen in the hunting field and at the rifle range. He was also a keen mountaineer, and spent several vacations climbing in the Dauphiné, where later he built a Chalet. Here he hunted chamois and in Sardinia moufflon.

He died within a short time of his wife, his devoted companion, who will also be remembered as the good friend of many generations of schoolboys.

WYNDHAM R. DUNSTAN.