OBITUARY NOTICES.

ERNEST FOURNEAU.

1872—1949.

ERNEST FRANÇOIS AUGUSTE FOURNEAU was born on October 4th, 1872, at Biarritz, which was also the natal city of the brothers Moureu, with whom he maintained a life-long friendship and by whom he was probably considerably influenced in the choice of a career. On leaving school in 1889 he was apprenticed in the pharmacy of Felix Moureu in Biarritz where he remained for nearly three years. Compulsory military service followed in 1892—1893, after which he proceeded to the École de Pharmacie in Paris, where he had among his fellow students Blaise and Valeur. In 1898 he obtained his diploma as a pharmacien, and then spent a year with Charles Moureu " passing in review most of the methods of organic chemistry." He completed his training with three years of research in Germany under Emil Fischer, Curtius, Gattermann, and finally Willstätter. In those days the production of pharmaceutical chemicals in Britain and France was virtually limited to the few alkaloids and glucosides in use in medicine and Germany was almost the sole source of supply of synthetic drugs. Fourneau returned to France determined to do his utmost to bring his country to the front in this branch of the fine chemical industry. He got the necessary opportunity in the research laboratories of Les Établissements Poulenc Frères, of which he was made Director in 1903 and where he remained until 1911 when Dr. Roux offered him a post as principal of a laboratory of therapeutic chemistry at the Pasteur Institute and in this congenial environment Fourneau passed the remainder of his working life.

While in Germany he published three papers : one with Emil Fischer describing the preparation of molecular anhydrides of amino-acids, such as glycylglycine hydrochloride (*Ber.*, 1901, **34**, 2868), and another with Willstätter on lupinine, in which the simpler empirical formula, $C_{10}H_{19}ON$, was adopted for the alkaloid and a beginning was made in the determination of its structure, which it was suggested consisted of a bicyclic system (*ibid.*, 1902, **35**, 1910) similar to that postulated for cinchonine, then under investigation by Königs and others; the third paper was by Fourneau alone on 9-phenyladenine, prepared by the general method of treating the appropriate trichloropurine with ammonia and reducing with hydriodic acid the resulting 6-amino-2 : 8-dichloro-9-phenylpurine (*ibid.*, 1901, **34**, 112).

In attempting an appreciation of Fourneau's work it must be remembered that he had a remarkable flair for envisaging the kind of molecular structure which would produce a particular pharmacological effect, that for him chemistry was applicable to a wide range of therapeutics, and that he was gifted with a notable capacity for taking pains to bring his ideas to practical fruition.

According to his own statement (*J. Pharm. Chim.*, 1910, [vii], **2**, 56) his work on amino-alcohols and their derivatives with therapeutic properties arose from the consideration that the two natural local anæsthetics, cocaine and tropacocaine, are *o*-benzoyl derivatives of the methyl ester of an amino-hydroxy-acid (ecgonine) and of an amino-alcohol (*pseudo*tropine) respectively. He thought it might be possible to accommodate these functions on a simpler nucleus to produce a substance having at least qualitatively a similar pharmacological effect. He also suggested that a simple nucleus might be devised on which a series of derivatives could be constructed with various therapeutic properties, *e.g.*, hypnotics, sedatives, antipyretics, etc.

The first series of amino-alcohols, represented by the general formula, $HO{\cdot}CMeR{\cdot}CH_2{\cdot}NMe_2$, prepared by Fourneau (*Compt. rend.*, 1904, **138**, 766) included six members in which R was represented by Me, Et, Pr^n, *iso*amyl, Ph, and $Ph{\cdot}CH_2$. In each case the benzoyl derivative formed a hydrochloride having local anæsthetic action. In the best of the series R was ethyl, and this compound on benzoylation and conversion into the hydrochloride became the well-known local anæsthetic stovaine, $Ph{\cdot}CO{\cdot}O{\cdot}CMeEt{\cdot}CH_2{\cdot}NMe_2,HCl$. Later, with Ribas (*Anal. Fís. Quím.*, 1927, **25**, 401) the amino-alcohol (stovaine base) was resolved into (+)- and (−)-forms and these were converted into (+)- and (−)-stovaines of which the former was the more potent local anæsthetic. Stovaine base was also condensed with anhydrous chloral, producing the semi-acetal $Me_2N{\cdot}CH_2{\cdot}CMeEt{\cdot}O{\cdot}CH(OH){\cdot}CCl_3$, which as the benzoate hydrochloride proved to be a potent local anæsthetic, although its salts were acid and too irritant for practical use (with Mlle. Brydona, *Bull. Soc. chim.*, 1928, [iv], **43**, 1023). An intensely active local anæsthetic was also obtained when benzoyl was replaced by *p*-aminobenzoyl in stovaine, as was done in preparing a series of homologues of novocaine $Et_2N{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}C_6H_4{\cdot}NH_2$ (with Puyal, *ibid.*, 1922, [iv], **31**, 424).

The second idea, that the pharmacological action might be varied by change in substituents, was also realised to some extent in this series, *e.g.*, the valeryl esters of the amino-alcohols were sedative and some of the esters with aromatic acids were antipyretics (*J. Pharm. Chim.*, 1910, [vii], **2**, 57) but these activities were either not well-developed or the derivative was toxic.

A later series (*ibid.*, pp. 337, 397) provided further evidence; it included derivatives of the simple aminomethylethylmethylcarbinol, $HO{\cdot}CMeEt{\cdot}CH_2{\cdot}NH_2$, corresponding to the stovaine base. This gave with valeryl chloride an amide $HO{\cdot}CMeEt{\cdot}CH_2{\cdot}NH{\cdot}CO{\cdot}CH_2{\cdot}CHMe_2$, with ethyl chloroformate a urethane $HO{\cdot}CMeEt{\cdot}CH_2{\cdot}NH{\cdot}CO_2Et$, and with propyl chloroformate the corresponding propyl ester. With potassium cyanate the same alcohol furnished the substituted urea $HO{\cdot}CMeEt{\cdot}CH_2{\cdot}NH{\cdot}CO{\cdot}NH_2$. The urethanes were hypnotic in action when given in large doses, *e.g.*, 0·4 g. per kg. of body weight in rabbits. It was suggested that their lower potency, compared with that of the similarly constituted amylurea

$$CH_3{\cdot}CH_2{\cdot}CMe_2{\cdot}NH{\cdot}CO{\cdot}NH_2,$$

is a result of their greater solubility in water owing to the presence of the alcoholic hydroxyl group.

At first, these amino-alcohols were obtained by treating with ammonia or amines the appropriate chlorohydrins prepared by Tiffeneau's method, the action of alkylmagnesium halides on chloro-ketones (*Compt. rend.*, 1902, **134**, 774), but later other methods were added; stovaine base, for example, was also made by the action of ethylmagnesium bromide on dimethylaminoacetone or by treating 2-ethyl-2-methylethylene oxide with dimethylamine (*J. Pharm. Chim.*, 1910, [vii], **2**, 109).

Ethylene oxides first became available with the preparation of β-methylstyrene oxide in 1905 (Klages, *Ber.*, 1905, **38**, 1969; Tiffeneau, *Compt. rend.*, 1905, **140**, 1458), and the study of their preparation, constitution, and reactions was continued by Fourneau and Tiffeneau and later by Fourneau and Ribas in a series of papers published from 1905 to 1927. When phenol is heated with epichlorohydrin in a closed tube, at least four products are formed, two of which are interconvertible, *viz.*, the oxide, phenylglycide ether $PhO{\cdot}CH_2{\cdot}CH\langle^{CH_2}_{O}$ and the chlorohydrin $PhO{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2Cl$. Similar glycide ethers from *p*-cresol and α-naphthol were described by Lindemann (*Ber.*, 1891, **24**, 2145). They all react with amines to form compounds of the type 3-dimethylamino-1-phenoxypropan-2-ol $PhO{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2{\cdot}NMe_2$, and Fourneau prepared a series (*J. Pharm. Chim.*, 1910, [vii], **1**, 55, 97) in which the phenoxy-group was replaced by *p*-tolyloxy, guaiacyl, thymyloxy, etc. All of them had antipyretic and analgesic properties but owing to their cardiac action they proved unsuitable for therapeutic use. This work was later (with Billeter and Bovet, *ibid.*, 1934, [viii], **19**, 49) extended to glycidic esters $\underset{\llcorner O \lrcorner}{CRR'{\cdot}CH}{\cdot}CO_2Et$, which with ammonia or primary amines in aqueous alcohol gave quantitative yields of the corresponding amides $\underset{\llcorner O \lrcorner}{CRR'{\cdot}CH}{\cdot}CO{\cdot}NR''R'''$. These, in experiments on rabbits, mice, and fish, showed a rapid narcotic action of short duration. The study was continued (with Billeter, *Bull. Soc. chim.*, 1940, [v], **7**, 593) as a detailed examination of the more complex action of ammonia, aliphatic amines, or arylamines on phenylglycidic esters.

Fourneau also prepared several series of amino-alcohols to ascertain the effect of changes in structure on pharmacological action, *e.g.*, the group of αγ-amino-alcohols, such as 1-dimethylaminohexan-3-ol, obtained by the action of dimethylamine on the chlorohydrins resulting from the interaction of chloropropaldehyde and the appropriate alkylmagnesium bromides. The hydrochlorides of the benzoates of these secondary alcohols showed anæsthetic action less durable than that of stovaine (with Mme. Ramart-Lucas, *ibid.*, 1919, [iv], **25**, 363; 1920, [iv], **27**, 386, 550).

Most of the amino-alcohols so far mentioned contain either a secondary or a tertiary alcohol group, and in 1930 in association with Mlle. Benoit and Firmenich (*ibid.*, 1930, [iv], **47**, 858) the investigation of this type of variation was completed with a series containing primary alcohol groups obtained by the action of methyl- or dimethyl-amine on the bromoacetins $R^1R^2C(CH_2Br){\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}CH_3$ resulting from the action of hydrobromic acid on diprimary glycols in acetic acid. The benzoates of these compounds were local anæsthetics but seemed to present no practical advantage over cocaine or stovaine with which they were compared.

The ephedrines, which Fourneau regarded as amino-alcohols rather than as alkaloids, occupied his attention at intervals from 1904 to 1945. Of the nine papers published on this subject several describe syntheses of ephedrines, and one (with Kanao, *ibid.*, 1924, [iv], **35**, 614) is of general interest as it included a useful bibliography of this subject up to that date, described

and discussed the reactions used in the various syntheses of the ephedrines, cleared up possible confusion between ephedrine and the *pseudo-* and *iso*-forms, and indicated which was formed in the various syntheses recorded. Later, with Barrelet (*Anal. Fis. Quím.*, 1929, **27**, 500) he synthesised three homologues of ephedrine and in 1945 (with Mlle. Benoit, *Bull. Soc. chim.*, 1945, [v], **12**, 985) described the interesting results of a study of the action of methylamine on the mixture of *cis-* and *trans*-forms of β-methylstyrene oxide formed when β-methylstyrene is treated with benzoyl peroxide. *iso*Ephedrine is usually the predominant product; ephedrine and *pseudo*ephedrine are also formed, but little or no *iso*-ψ-ephedrine.

Among other types of local anæsthetics may be mentioned a series derived from piperazine and made by the interaction of piperazine hydrate and ethylene oxides—for example, 1-(2-hydroxy-2-methyl-*n*-butyl)piperazine HO·CMeEt·CH_2·N<$[CH_2]_4$>NH and the disubstituted bis-compound HO·CMeEt·CH_2·N<$[CH_2]_4$>N·CH_2·CMeEt·OH, both made from ethylmethylethylene oxide (with Barrelet, *ibid.*, 1929, [iv], **45**, 1172) and of which a higher homologous series was made (with Samdahl, *ibid.*, 1930, [iv], **47**, 1003). These substances from the butyl derivatives upwards were definitely local anæsthetics but some of them proved irritant to the mucous membrane and the cornea. Finally it was found that phenanthrols are converted by 2-diethylaminoethyl chloride into amino-ether oxides (with Matti, *ibid.*, 1940, [v], **7**, 615; 1942, [v], **9**, 633), of which the 1-, 2-, 3-, 4-, and 9-2′-diethylaminoethoxyphenanthrenes were prepared and also the 9 : 10-disubstituted product. The mono-series proved to be local anæsthetics but none was analgesic; the disubstituted substance produced intense anæsthesia when applied to the tongue. The more interesting observation was also recorded that while the monosubstituted products were cardiac sedatives and lowered excitability of the myocardium, the single disubstituted product obtained, viz., 9 : 10-bis(diethylaminoethoxy)phenanthrene dihydrochloride, was very toxic.

Of the two bases, ψ-tropine and ecgonine, which Fourneau had in mind as models when the work on local anæsthetics was started, all products so far described are based on the ψ-tropine or amino-alcohol type. Work on the ecgonine or amino-hydroxy-acid type was much less fruitful. The first acid used was phenyl-lactic acid (*ibid.*, 1907, [iv], **1**, 549); " the benzoyl derivatives of ethyl phenyldimethylaminolactate Me_2N·CH(CO_2Et)·CHPh·O·COPh " was an effective local anæsthetic but too acid for practical use. Attention was then given to hydroxy-*iso*butyric acid : the propyl ester of the derived chloro-derivative was converted into propyl β-dimethylamino-α-hydroxy*iso*butyrate of which the valerate Me_2N·CH_2·CMe(CO·OC_3H_7)·O·CO·C_4H_9 as the hydrobromide had some success as a hypnotic under the name " Quietol " although the benzoyl derivative of the ethyl ester, which had intense anæsthetic properties when applied to the tongue, like the previous compound, was too acid for use (*J. Pharm. Chim.*, 1908, [vi], **27**, 513; *Bull. Soc. chim.*, 1909, [iv], **5**, 229); and the insertion of a second dimethylamino-group failed to overcome this difficulty (*ibid.*, 1921, [iv], **29**, 413).

Apart from the hypnotics arising out of the work described above, Fourneau also investigated certain other series providing such drugs, notably the ureides of bromovaleric acids on which three comprehensive papers were published (with Florence, *ibid.*, 1927, [iv], **41**, 1518; 1928, [iv], **43**, 211, 1027), dealing especially with the interrelations of chemical structure and hypnotic action. It was found in a comparative study using the known α-bromo*iso*valerylurea, $CHMe_2$·CHBr·CO·NH·CO·NH_2, and α-bromo-α-ethylbutyrylurea, CEt_2Br·CO·NH·CO·NH_2, as reference standards, that the effect of displacement of the bromine atom in the chain, and accumulation of bromine atoms, confirmed the relation already observed by Overton between the partition coefficient in oil and water and the hypnotic properties, and supported Tiffeneau's statement that the relation holds only within the same series. Migration of the bromine atom from the α- to the β-position reduced the hypnotic action, the partition coefficient, and the solubility in water, but it was concluded later that the α-position of the bromine atom is not specific, active ureides with the bromine in β- and γ-positions being also found. Branching in the chain produced a marked increase in solubility in water and in the partition coefficient, and in this series the partition coefficient and hypnotic action were closely parallel.

Among other series of pharmacologically active compounds prepared and investigated by Fourneau, were derivatives of benzodioxan and aminocoumarans, which simulate the sympathicolytic action of yohimbine and ergotamine (with Maderni and Mme. de Lestrange, *J. Pharm. Chim.*, 1933, [viii], **18**, 185), of which the most interesting appeared to be 3-diethylaminomethylbenzodioxan which suppresses and reverses the vasoconstrictive action of adrenaline and induces lowering of body temperature in rabbits (with Bovet, *Compt. rend. Soc. Biol.*, 1933, **113**, 388). Attention was also directed to the intense acetylcholine type of activity shown in a series of amino-acetals of polyhydric alcohols, which is at its peak in 2 : 3-ethylidenedioxy-

propyltrimethylammonium iodide (I; R = H, R′ = Me) (with D. Bovet, F. Bovet, and Montézin, *Bull. Soc. Chim. biol.*, 1944, **26**, 516). This line of work was then extended to the examination of muscarine-like action in amino-acetals of the general types (I) and (II). All the examples examined showed this type of action, which reached a maximum in type (I) with R = H and R′ = Me, and in type (II) with R = H, but fell off when R or R′ was increased and disappeared when R = R′ = Ph. It was also reduced by the insertion of a hydroxyl group (with Bovet, Montézin, J. P. Fourneau, and Mlle. Chantalou, *Ann. Pharm. Franç*, 1944, **2**, 120; 1945, **3**, 114). This was followed by a paper dealing with the complex reactions, simulating those of nicotine, muscarine, and curare, shown by a series of halogenated derivatives of alkyltrimethylammonium salts (with D. Bovet and F. Bovet, *ibid.*, 1946, **4**, 166).

(I) $I\{Me_3N\cdot CH_2\cdot CH(O\cdot CRR'\cdot O)\cdot CH_2$ $\qquad$ $I\{Me_3N\cdot CH_2\cdot CH(O\cdot CHR\cdot O)\cdot CH_2$ (II)

The work so far mentioned relates almost wholly to symptomatic drugs, but Fourneau also made notable contributions to chemotherapy proper. In the early years of this century great interest was aroused by Thomas's successful treatment of trypanosomiasis in animals with atoxyl (*Proc. Roy. Soc.*, 1905, *B*, **76**, 589) which was shown by Ehrlich and Bertheim to be sodium hydrogen *p*-aminophenylarsonate, $p\text{-}NH_2\cdot C_6H_4\cdot AsO(OH)\cdot ONa$ (*Ber.*, 1907, **40**, 3292), and they in common with Fourneau (*J. Pharm. Chim.*, 1907, [vi], **25**, 332, 528) agreed that it was first made by Béchamp in 1863. This inaugurated a period of great activity, during which the important drug " Salvarsan " was discovered in Germany, and Ehrlich and Hata published their conclusions on the therapeutic superiority of organic arsenical compounds containing arsenic in the tervalent form over the phenylarsonic acid series in which arsenic is quinquevalent (Die experimentelle Chemotherapie der Spirillosen, Berlin, 1911). Fourneau gave reasons for disagreement with these views and promised further work on the subject (*Ann. Inst. Pasteur*, 1921, **35**, 571). The results were published in two remarkable papers (*ibid.*, 1923, **37**, 551; 1926, **40**, 933) in which he had as colleagues M. Navarro-Martin, M. and Mme. Tréfouel, and Mme. de Lestrange-Trévise. The preparation of a large number of arsenical compounds, many of them already known, was described and there was recorded for each the maximum tolerated dose and the effective curative dose in animals infected with trypanosomes or spirochætes. The effects, on efficiency against each type of infection, of the nature and orientation of each substituent alone or in conjunction were discussed in detail. Among the points stressed by Ehrlich and Hata against quinquevalent arsenic compounds was their liability to cause nervous disorders including ocular trouble, and Fourneau was at pains to point out that as a number of his compounds did not produce these effects in the experimental animals this kind of action could not be attributed to the arsonic acid group. Among the compounds dealt with were the ten isomeric aminohydroxyphenylarsonic acids, which were fully described later, with a comparison of their pharmacological constants (with M. and Mme. Tréfouel and Mlle. Benoit, *Bull. Soc. chim.*, 1927, [iv], **41**, 499), and one of these in the form of its *N*-acetyl derivative, *viz.*, 3-acetamido-4-hydroxyphenylarsonic acid, is the well-known drug " Stovarsol " which was adopted in the British Pharmacopœia in 1936 under the name acetarsol. The drug now seems to be used principally for the treatment of amœbiasis and *Trichomonas vaginalis* and for congenital syphilis in young children because it can be administered orally.

It should be noted that 3-amino-4-hydroxyphenylarsonic acid had already been made by Ehrlich and Bertheim (*Ber.*, 1912, **45**, 756) during their preparation of " Salvarsan," but its recognition as the basis of a useful drug was undoubtedly the result of the careful work of Fourneau and his colleagues on its preparation and pharmacological action. The series also included " Orsanine," 4-acetamido-2-hydroxyphenylarsonic acid, which was rather more toxic than " Stovarsol " and unlike the latter is an effective trypanocide (cf. Walls, *Chem. and Ind.*, 1951, 607).

Among other arsenic compounds prepared by Fourneau may be mentioned the optically active forms of methyltryparsamide (*N*-*p*-arsonophenyl-β-methylglycine amide, $NH_2\cdot CO\cdot CHMe\cdot NH\cdot C_6H_4\cdot AsO_3H_2$), obtained by the use of quinine, which were used for the resolution of synthetic (±)-ephedrine (with Nicolitch, *Bull. Soc. chim.*, 1928, [iv], **43**, 1232).

Special interest also attaches to the series of diarsonic acid derivatives of various aryl nuclei, which exhibited a reversal of the trypanocidal action of the monoarsonic acids, being active against *T. congolense* but inactive towards *T. brucei* (with M. and Mme. Tréfouel, Bovet, and

Koetschet, *Compt. rend.*, 1933, **196**, 1173) and to the so-called " alcoholic arsonic acids," such as 4-amino-3-hydroxymethylphenylarsonic acid, $NH_2 \cdot C_6H_3(CH_2 \cdot OH) \cdot AsO_3H_2$, which in pharmacological tests in mice proved 3—4 times as active as atoxyl, indicating that the $CH_2 \cdot OH$ group had a favourable influence on trypanocidal action (with Mme. de Lestrange, *Bull. Soc. chim.*, 1933, [iv], **53**, 330).

Fourneau also published five papers on organic mercury compounds of which two with K. I. Melville (*J. Pharm. exp. Ther.*, 1931, **41**, 21, 47) deal with mercurial chemotherapy, the first being a study of the evaluation and mechanism of mercurial toxicity in rabbits and the correlation of the various types of this action with chemical structure in the four groups of compounds tested. In the second paper a method is developed for the quantitative determination of the diuretic activity of mercurial compounds by intravenous injection into rabbits, the results being expressed in the form of a chemotherapeutic coefficient. All the soluble mercury compounds tested were active, but no well-defined relation between degree of activity and chemical structure was found.

Fourneau and his colleagues, M. and Mme. Tréfouel, also made important contributions to the chemotherapy of malaria. They first examined the biological method of estimating the efficacy of an antimalarial drug, involving the use of canaries experimentally infected with avian malaria (*Plasmodium relictum*), and, having developed a standard method (with Stefanopoulo, Mlle. Benoit, Mme. de Lestrange, and K. Melville, *Ann. Inst. Pasteur*, 1930, **44**, 503), tried it out on a few known antimalarial drugs including plasmoquin, which had become available in 1926, and then proceeded to apply the test to well over 100 substances of varied types, including complex amino-alcohols, several kinds of quinoline derivatives, and organic compounds of antimony, arsenic, lead, and mercury. The preparation of these compounds was described separately (with Mlle. Benoit, *ibid.*, p. 719; with Wancolle, *Bull. Soc. chim.*, 1930, [iv], **47**, 738). This investigation may be regarded as a preliminary screening test and it afforded no positive results of importance. In two further papers (with Bovet and Mlle. Benoit, *Ann. Inst. Pasteur*, 1931, **46**, 514; 1933, **50**, 731) a series of substituted quinolines of the plasmoquin type were used in biological tests on the Java sparrow or rice finch (*Orizonis orizivora*), which always carries a natural infection of *Hæmoproteus orizivoræ* similar in type to the malaria parasite. The substances used were mainly 6-alkoxy-8-aminoquinolines derivable from the general formula $RO \cdot Q \cdot NH \cdot [CH_2]_n \cdot NR'_2$. $[CH_2]_n$ was also in many cases changed to a branched chain or a branched oxygenated chain, either of which had a dystherapeutic effect. Among a number of promising compounds final choice was made of 8-3′-diethylaminopropylamino-6-methoxyquinoline which had a chemotherapeutic index of 1 : 100 compared with 1 : 40 recorded for plasmoquin (side-chain $\cdot NH \cdot CHMe \cdot [CH_2]_3 \cdot NEt_2$) in the same series of tests. This substance, first distinguished as F710, was subsequently named " Rhodoquine " in France and later " Plasmocide " in Russia.

Two other drugs of German origin also attracted Fourneau's attention. In 1921 biological and clinical reports began to appear about a new and effective trypanocide, Bayer 205, the chemical structure of which was not disclosed. It aroused intense curiosity and was investigated by Fourneau and his colleagues, who assigned to the drug the now well-known formula and described the preparation of F309, which was soon generally accepted as identical with Bayer 205 (with M. and Mme. Tréfouel and Vallée, *Compt. rend.*, 1924, **178**, 675). A full account of the drug including a review of the already extensive literature was given as an introduction to a description of their own researches on ureas of aminobenzamidonaphthalenesulphonic acids, for which the results of biological tests with comments on the variation of these with changes in chemical structure were recorded, the most interesting feature being in some cases the large effect on trypanocidal action induced by a small deviation in structure (*Ann. Inst. Pasteur*, 1924, **38**, 81). The second drug was " Prontosil," 2 : 4-diamino-4′-sulphamylazobenzene hydrochloride, to which attention was first called by Domagk's paper (*Deut. med. Woch.*, 1935, **61**, 250) describing its action on mice infected with hæmolytic streptococci. After it had been shown (M. and Mme. Tréfouel, Nitti, and Bovet, *Compt. rend. Soc. Biol.*, 1935, **120**, 756) that the antibacterial action of this drug was probably due to its breakdown in the body into sulphanilamide, which they found to be active against streptococci in the mouse and rabbit (cf. Buttle, Gray, and Stephenson, *Lancet*, 1936, **230**, 1286), considerable interest was aroused in the investigation of the range of activity of sulphanilamide and its analogues and derivatives, to which Fourneau and his group made two important contributions (*Compt. rend. Soc. Biol.*, 1936, **122**, 258, 652). In the first they dealt with the action of 130 compounds, all related to or analogous with sulphanilamide, and showed that changes in the character, or orientation of the two substituents, or addition of a third, usually reduced or even abolished streptococcidal

action, which however was retained after diazotisation and coupling. The second paper dealt with the inhibition of moulds which was found to run parallel with the action on streptococci.

The same group of workers then began work on other sulphur compounds (*Compt. rend.*, 1937, **204**, 1763; **205**, 299) and recorded that in the 4 : 4′-dinitrodiphenyl series the sulphide and disulphide were active but inferior to sulphanilamide, whereas the sulphone was more active than the latter against streptococcal infection in mice. It was also active, in higher doses, against pneumococcal septicæmia. About the same time the dinitro- and the diamino-sulphones were under examination in England by Buttle, Stephenson, Smith, Dewing, and Foster (*Lancet*, 1937, **232**, 1331). Their results were in general agreement with the French findings for the dinitro-compound, but they were much more concerned with the more toxic diamino-derivative, which proved to be 100 times as active as sulphanilamide against streptococcal infections and was also effective in prolonging the lives of mice infected with pneumococcus. The obstacle to therapeutic use of this new and potent antibacterial agent was its toxicity and this was overcome when the French group investigated the diacetyl derivative, di-(*p*-acetamidophenyl) sulphone, which they found to be 10 times as active as sulphanilamide against either streptococcal or pneumococcal infections in mice; it was also much less toxic than the parent diamino-compound.

As every chemist knows, there have been enormous developments from these early observations and to-day there is almost a special section of therapeutics based on what are colloquially called " sulpha " and " sulphone " drugs.

In addition to the work on ephedrine already referred to, Fourneau was concerned with two other alkaloids, Hesse's quebrachine, which was identified as yohimbine (with Page, *Bull. Sci. Pharmacol.*, 1914, **21**, 7), and corynanthine; the latter he isolated from *Pseudocinchona africana*, and showed that it was isomeric with yohimbine (*Compt. rend.*, 1909, **148**, 1770; with Fiore, *Bull. Soc. chim.*, 1911, [iv], **9**, 1037) and yielded on acid hydrolysis corynanthic acid. On alkaline hydrolysis an acid of lower rotation was produced, which on methylation did not reproduce corynanthine, but according to some authorities a mixture of corynanthine and yohimbine (*Compt. rend.*, 1910, **150**, 976; with Mlle. Benoit, *Bull. Soc. chim.*, 1945, [v], **12**, 934).

The last paper Fourneau published was written with Professor Janot and dealt with the chemistry of the curares, the *Erythrina* alkaloids, and synthetic substances exhibiting a curare-like action (*Ann. Pharm. Franç.*, 1948, **6**, 406; 1949, **7**, 353), and to add to the value and exhaustive character of this useful review it was accompanied by a historical and botanical section contributed by Paris (*ibid.*, 1949, **7**, 346) and a chapter on the standardisation of curares by Cheymol and Mlle. Corteggiani (*ibid.*, p. 368). It included an account of the action of " Flaxedil," 1 : 2 : 3-$C_6H_3(O{\cdot}CH_2{\cdot}CH_2{\cdot}NEt_3\}I)_3$, one of a series of phenolic ethers of quaternary ammonium bases possessing curare-like properties, described by Mme. de Lestrange (*ibid.*, 1948, **6**, 450) and examined pharmacologically (Bovet, Depierre, and Mme. de Lestrange, *Compt. rend.*, 1947, **225**, 74) with results promising enough to warrant therapeutic trials in France and in England (see, for example, Mushin, Wien, Mason, and Langston, *Lancet*, 1949, **256**, 726; Doughty, *ibid.*, 1950, **258**, 899).

There are a number of other investigations to which limitation of space precludes reference, but the foregoing account is probably sufficient to indicate the wide range of Fourneau's interests and his unique capacity for dealing with chemotherapeutic problems. In spite of his preoccupation with experimental work he found time to write numerous reviews on special drugs, such as the two on organic arsenical compounds and curare already referred to, and he frequently contributed reports on the current prospects of and developments in chemotherapy to special Congresses, such as that on " The Relations between the Chemical Constitution of Compounds and their Therapeutic Action " submitted to the 6th International Chemical Congress held at Bucarest in 1925. In the bibliography appended to his admirable " Notice sur la Vie et les Travaux de Ernest Fourneau " (*Bull. Soc. chim.*, 1950, 953) Professor Delépine has published a list of thirty such reviews contributed by Fourneau from 1902 to 1949. Fourneau was also much concerned for the progress of the pharmaceutical industry, especially in France, as evidenced by his writings on patents and on the organisation of research in chemotherapy.

He did not lack appreciation of his work during his lifetime, for he received many honours both in France and abroad, and the memoirs published since his decease on the 5th August, 1949, bear witness not only to great achievements in his chosen subject but also to the personal inspiration, which attracted and retained for so long a group of devoted colleagues and disciples.

T. A. Henry.

ALBERT EDWARD GILLAM.

1900—1950.

THE death of Dr. A. E. Gillam occurred, after a long illness, at his home in Timperley, Cheshire, on January 16th, 1950.

Although never having received an academic training in the usual sense, he rose, by dint of exceptional endeavour and great enthusiasm, from being a laboratory assistant in Liverpool to the position of senior lecturer at Manchester University at the time of his death. Gillam was a pioneer in the use of ultra-violet absorption spectra for the solution of analytical and structural problems in organic chemistry, and his contributions have assisted materially in paving the way for the truly remarkable use made of these methods today.

Gillam joined the laboratory staff of the Department of Inorganic Chemistry in the University of Liverpool, then under the direction of Professor E. C. C. Baly, immediately after leaving school. He eventually became principal lecture demonstrator and in the evenings he studied at the Central Technical School, obtaining the Associateship of the Royal Institute of Chemistry in 1926, and subsequently becoming a part-time assistant lecturer at the College. Alongside his work as lecture demonstrator he began research under the direction of Professor R. A. Morton and studied the absorption spectra of halogens and interhalogen compounds (*Proc. Roy. Soc.*, 1929, *A*, **124**, 604), methods of determining ultra-violet light intensity (*J. Soc. Chem. Ind.*, 1927, **46**, 417), and other related topics. He was awarded the M.Sc. degree in 1929 for an outstanding thesis on this work.

In due course, under Professor Sir Ian Heilbron and Professor R. A. Morton, Gillam became associated with those pioneering studies in the application of ultra-violet and visual light absorption measurements to the chemistry of natural products, an application which in the past two decades has proved so fruitful. He played an important part in the development of the now well-known methods of estimating vitamin A and carotene (*Biochem. J.*, 1931, **25**, 30, 1346, 1352), introducing a modified method of determining the butter-fat content of these substances (*Biochem. J.*, 1934, **28**, 79). This work led directly to one of Gillam's most significant contributions to organic chemistry. In Manchester with El Ridi in 1935, he made the pioneer observation of the occurrence of geometrical isomerism in the series of C_{40} carotenoids, an observation which was followed by the extensive fundamental development of this subject in the hands of Zechmeister and his school. During an examination of the carotenoids present in butter unsaponifiable matter, the extracted pigments were fractionated by adsorption on alumina and examined spectroscopically, and at first it appeared that the β-carotene present was accompanied by appreciable quantities of α-carotene (*Biochem. J.*, 1936, **30**, 1735). Separate experiments with the pure β-isomer then led to the conclusion that β-carotene underwent a reversible change into another pigment on adsorption on alumina. Subsequently the new pigment was isolated in a pure condition by repeated chromatography, and it was named *pseudo*-α-carotene, because of its spectroscopic similarity to the α-isomer. The isomerisation of α-carotene was also studied (*Biochem. J.*, 1937, **31**, 1605) and another new pigment, *neo*-α-carotene, was isolated and characterised. It was initially concluded that the change apparently brought about by the adsorption process involved either the migration of a double bond out of conjugation or else geometrical isomerism, the latter explanation subsequently being preferred after the discovery that isomerisation of α-carotene resulted in little change in the growth-promoting activity. Gillam's work in this field was closely followed by that of Zechmeister and Tuzson (*Biochem. J.*, 1938, **32**, 1305) who, finding that lycopene and cryptoxanthin isomerised spontaneously in solution, suggested that such was also the case with the carotenes, the adsorption procedure serving only to separate the preformed mixture of isomers. This suggestion was fully confirmed by Carter and Gillam (*Biochem. J.*, 1939, **33**, 1325), an equilibrium mixture of β-carotene (70%) and *pseudo*-α-carotene (30%) being found to be produced when the former was heated in benzene at 80° for three hours. Some idea of the extent of the ultimate development of this work can be gleaned from the review by Zechmeister (*Chem. Reviews*, 1944, **34**, 267).

In 1940 Gillam published the first paper (with Booker and Evans, *J.*, 1940, 1453) in a series in which it was " planned to collect experimental data on the absorption spectra of compounds containing specific light-absorbing groups of atoms with the object of discovering the effect of various well-defined molecular environments on the resulting absorption spectra." It was pointed out for the first time that the absorption spectra of conjugated dienes were affected by the degree of substitution of the chromophoric system. Thus hexa-2 : 4-diene absorbs

maximally at 2270 Å, the two terminal methyl groups being responsible for the shift of 100 Å from the position of absorption of the parent butadiene. A similar state of affairs was found to exist in the αβ-unsaturated ketones (Evans and Gillam, *J.*, 1941, 815). These studies, simultaneous with the more extensive treatment by Woodward (*J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 72) and the further extension by Fieser and Fieser (cf. " Natural Products Related to Phenanthrene," 1949, p. 184) to the steroid series, whereby widely applicable rules have been enunciated relating position of maximal absorption to degree of substitution, have materially assisted the organic chemist in tackling structural problems.

Gillam first investigated absorption spectra of terpenoid compounds in association with Professor Sir John Simonsen, it being demonstrated that the sesquiterpene ketone, α-cyperone, like eremophilone, was αβ-unsaturated (*J.*, 1936, 676). With T. F. West, the investigation, by spectrographic methods, of a number of hitherto obscure structural problems was later undertaken. These studies included the elucidation of the nature of the chromophoric system in irone (*J.*, 1942, 95) and the observation and discussion of the peculiar light-absorption properties of umbellulone (*J.*, 1945, 95). As a result of a study of isothujone (*J.*, 1941, 811) the distinctly anomalous absorption properties of unsaturated ketones containing a five-membered ring were noted, the maxima being at about 100 Å to shorter wave-lengths than the calculated values, one of the few instances where the Woodward rules do not apply.

Gillam and West made an important contribution to the determination of the structure of the pyrethrins, the potent insecticidal constituents of pyrethrum flowers (*J.*, 1942, 71; 1944, 49). They demonstrated, in a particularly elegant manner, that the light-absorption properties of the ketonic hydrolysis product, pyrethrolone, resulted from the presence in the molecule of a side-chain conjugated-diene chromophore in addition to an αβ-unsaturated ketone system contained in a five-membered ring. These two systems give rise to additive absorption in the 2280-Å region but, by use of subtraction methods and the light-absorption data for the ketone and the tetrahydro-ketone and their respective semicarbazones, conclusive evidence of the presence of a disubstituted conjugated-diene system, absorbing at about 2260 Å was obtained.

Gillam came with Heilbron to Manchester as a research assistant in 1933 and then was appointed special lecturer in 1935. He was awarded the D.Sc. degree of Liverpool University in 1937 and promoted to senior lecturer in 1946. In Manchester Gillam was responsible for the supervision of all the routine spectrographic work of the rapidly growing research department, an activity which afforded him much scope and the opportunity of increasing greatly the range of substances examined. In addition to work on the polyenes, including vitamin A and the carotenoids, he encountered steroids, triterpenes, and synthetic compounds of many types, and his able and willing collaboration is acknowledged in many of the papers published from Manchester during this period. His assistance was indeed willingly given and he devoted much time, which he could doubtless have well used in pursuing his own problems, to helping research students and his colleagues with theirs. Always the careful investigator, fully conscious of the limitations of the technique he employed, Gillam could never be persuaded to allow his results to support conclusions which he did not feel were amply justified, and wishful thinking on the part of his associates was kindly but firmly discouraged.

For many years Gillam was responsible for the teaching of chemistry to Manchester medical students, an arduous and often unrewarding task which he discharged in a characteristically efficient manner. He was a meticulous teacher, remarkably patient and sympathetic. He served as local representative of the Chemical Society for six years, and for the Bureau of Abstracts he undertook in 1946 the onerous task of compiling the new formula index. His interest in nature study was deep and his knowledge extensive, particularly in ornithology.

Gillam will long be remembered in Manchester as a loyal, helpful, and unfailingly courteous colleague. His courage and cheerfulness made a lasting impression on those who saw him in his last few months. He left a widow and two sons, the elder of whom will soon be going to the University to study chemistry.

E. R. H. Jones.

HEINZ PETER KOCH.

1918—1951.

THE tragic death of Peter Koch in a mountaineering accident on Snowdon on March 24th has removed from our midst a young scientist who, by virtue of his ability as an organic chemist and his wide experience of the application of spectrographic methods, seemed destined to make valuable contributions to the advancement of chemistry.

Koch was born in Germany in 1918 and he came to this country with his parents in 1935. After two years at St. Paul's School he gained an Entrance Scholarship to Imperial College of Science and Technology where he graduated with First Class Honours in 1939, being awarded the Hofmann Prize for Organic Chemistry. He began research under the direction of Professor Sir Ian Heilbron and one of the writers in 1939 and, in spite of considerable interruption and the necessity, common in those days, of changing his subject owing to the exigencies of war-time requirements, he completed a thesis and obtained the degree of Ph.D. in 1942 (see *J.*, 1942, 393, 735). His interest in spectrography began at that time in a desire to explain some of the anomalous light-absorption results which were noted during the work. Arising out of studies on acetylmethyl*cyclo*hexene, Koch discussed (*Chem. and Ind.*, 1942, **61**, 273) the light absorption of geometrical isomerides and its implications in relation to the stereochemical structure of vitamin D. Some of the ideas emanating from this earlier work have since been extended in many laboratories and, in particular, mention might be made of a comparatively recent joint publication (*J.*, 1949, 1890) concerned with the development of the concept of steric inhibition of resonance in natural and synthetic derivatives of *cyclo*hexene.

In 1942, Koch joined the British Rubber Producers' Research Association and proceeded to apply spectroscopic methods of analysis and structural investigation to a variety of chemical problems. Naturally concerned at first with ultra-violet absorption, he later—after a period of secondment to Dr. G. B. B. M. Sutherland's laboratory at Cambridge—installed an infra-red spectrometer, and the resulting measurements and their interpretations became his primary interest from about 1947 onwards. The definitive value of spectroscopic data in his new sphere was soon apparent; his first joint publication from the Welwyn laboratories (*J.*, 1943, 472) established conclusively, and far more simply than could be done by chemical means, that chromans were the products of reaction between olefins and saligenin. Subsequently his work fell roughly into three groups: (i) the determination of the ultra-violet and infra-red spectra of olefins and related compounds, and their correlation in terms of electronic and stereochemical structural factors; (ii) the essentially analytical problems concerned with tracing double-bond displacements during olefinic reactions; and (iii) an extensive spectroscopic study of organic sulphur compounds. Notable work in the first group is that on glutaconic ester derivatives (*J.*, 1945, 216), on dicinnamyl and related compounds (*J.*, 1948, 1111, 1118, 1123), and a comprehensive investigation of double-bond structure in simple acyclic terpenes (*J.*, 1950, 915). The second group includes studies of the isomerisations accompanying autoxidation (*J.*, 1943, 541; 1945, 445) and bromination with *N*-bromosuccinimide (*J.*, 1950, 936, 3051). The third group comprises impressive contributions to our knowledge of the spectral and structural properties of a diverse collection of sulphides, sulphoxides, and sulphones (*J.*, 1949, 387, 394, 401, 408, 2442; *Trans. Faraday Soc.*, 1951, **47**, 7). Quite a different subject was discussed in his last paper, *viz.*, the infra-red spectra of tropolone and some of its derivatives and their constitutional requirements (*J.*, 1951, 512).

Koch was appointed to a senior lecturership at Manchester University from January 1951, but he did not commence his duties until March. He had been collaborating with workers in the Organic Chemistry Department there for some time previously in spectrographic studies resulting in the publication of a detailed paper on the infra-red spectra of a wide range of unsaturated steroids (*J.*, 1951, 2402). Although at Manchester University for only a few weeks, Koch had already made a most favourable impression, both scientifically and personally. His exceptional perspicacity over a broad field of scientific interest was a source of admiration to his co-workers and other colleagues and will long be remembered by them.

L. BATEMAN.
E. R. H. JONES.

ALEXANDER McKENZIE, M.A., D.Sc., LL.D., F.R.S.

1869—1951.

ALEXANDER McKENZIE was born in Dundee on December 6th, 1869. His father, Peter Mitchell McKenzie was a good representative of the old type of Scottish " dominie," a man with varied interests. The boy's early education was received in his father's school first in Dundee, and then at Tealing. In 1882 he went to the High School of Dundee, having already made a start in Latin, Greek, French, and Mathematics. He joined the " classical " side of the school and, in 1885, was the Edinburgh Angus Club Medallist in Latin. When only 15 years old, he entered United College, St. Andrews, and laid a sure foundation for his liberal outlook of later life by reading for the pass M.A. degree. Gradually, particularly under the influence of Purdie, his scientific interest developed. He graduated B.Sc. in 1891 with Chemistry and Natural Philosophy as principal subjects. He was placed in the First Rank of Honours in nearly all his subjects. The thrill of research soon captivated him and, after working under Purdie for a while he gave up, at considerable personal sacrifice, his lectureship at United College to work with Marckwald in Berlin. He graduated Ph.D in 1901, and shortly afterwards graduated D.Sc. at St. Andrews. From February 1901 until October 1902 he held the Grocers' Company's Research Studentship in the Lister Institute, during which period he was engaged entirely in research in Harden's laboratory. From 1902 to 1905 he worked at Birmingham University under Professor P. F. Frankland, becoming Special Lecturer in Organic Chemistry. In 1905 he was appointed to the Headship of the Chemistry Department of Birkbeck College, London. He brought with him a well-considered plan of research and quickly gathered round him an enthusiastic band of co-workers at first drawn mainly from his younger colleagues and gradually augmented by senior students as the department developed. From 1914 to 1938 McKenzie was Professor of Chemistry in University College, Dundee. His researches expanded and developed throughout the field of stereochemistry and his reputation became world-wide. At home, the merit of his work was recognised by his election in 1916 as a Fellow of the Royal Society, and in Germany by the rare distinction of his admission as an Honorary Fellow of the Kaiserliche Deutsche Akademie der Naturforscher, Halle. On his retirement he received the LL.D. of St. Andrews. His interest in Chemistry continued after his retirement. He died peacefully, sitting in his armchair in the study, surrounded by the books he loved so much.

Another lifelong interest which McKenzie acquired at St. Andrews was golf. He became Secretary of the Golf Team. When in Berlin he won his way into the final for the championship of Germany and, in 1903, he was a semifinalist in the Amateur Scottish Golf Championship at Monifieth.

McKenzie was an exceedingly able organiser and administrator. His lectures were lucid and interesting and always brought very carefully up to date. His relationships with his research students were very happy and he had an instinctive knowledge of the amount of help and encouragement which each required. He took a lively and enduring interest in the personalities and progress of his pupils, an interest which he maintained throughout his years of retirement.

Professor McKenzie was married in 1906 to Miss Alice H. Sand and there is one son, Duncan Buchanan, who is with the Ministry of Supply.

McKenzie's researches were mainly concerned with stereochemical problems. His inaugural dissertation (Berlin, 1901) has become a classic, and if the suggested resolution of a racemic acid by partial esterification with an optically active alcohol is due to Marckwald, it may be justly claimed that the ultimate isolation of pure (—)-mandelic acid by this method could not have been achieved without the intimate knowledge of the chemistry of the acid which McKenzie acquired at St. Andrews. The counterpart of this method, the fractional hydrolysis of (—)-menthyl (±)-mandelate by alkali, proved a more difficult problem, involving processes of racemisation which were not understood until several years later. This work was subsequently extended to the partial resolution of (±)-*sec.*-octyl alcohol by (+)-tartaric acid, of (±)-mandelic acid by (—)-borneol, of (±)-α-naphthylglycollic acid and of (±)-*o*-nitromandelic acid by (—)-menthol; to the partial hydrolysis of (—)-bornyl (±)-lactate and other esters.

The value of McKenzie's work on the Walden inversion lies on the experimental side in showing how very general the action is and how it can be applied to different types. His work in the mandelic acid group was followed by the interconversion of the optically active atrolactinic acids which proved that the Walden inversion can occur with a compound which

has no hydrogen atom in direct attachment to the asymmetric carbon atom. Further important results include the proof of the difference in the action of phosphorus pentachloride and thionyl chloride in displacing hydroxyl, the observation that a Walden inversion can occur with an optically active ester, with a β-hydroxy-acid, and with an optically active alcohol. The " displacement racemisation " which occurs to a greater or less extent when a group attached to an asymmetric carbon atom is substituted by another group was examined in considerable detail and the semipinacolinic change was brought into the sphere of the Walden inversion. A hypothesis of the mechanism of the Walden inversion was based on the conception that addition precedes substitution and that an optically active structure containing a tervalent carbon atom can possess a transient existence without losing its optical activity. Several examples of such retention were observed.

McKenzie contributed greatly to the literature of catalytic and displacement racemisation. He brought much experimental evidence of the intimate relationship between keto-enolic desmotropy and racemisation by alkali, adduced examples of the racemisation of esters before their hydrolysis, and established the great susceptibility of acid amides. (Had he known at that time how readily the optically active mandelamides are racemised, it is doubtful if he would have attempted the preparation of the optically active benzoins.) He made many studies of the action of nitrous acid on amino-alcohols and of the dehydration of glycols.

A chance observation that 1-amino-2-hydroxy-1 : 2 : 2-triphenylethane is converted by nitrous acid, not into the corresponding glycol but into phenyldeoxybenzoin led McKenzie to examine the migration of hydrocarbon radicals in optically active compounds, a process which he named " semipinacolinic deamination." The most interesting application is that for the preparation of optically active ketones. A further important application lies in its use for contrasting the migrational aptitude of two different hydrocarbon radicals.

McKenzie's first asymmetric synthesis was that of (−)-atrolactinic acid, carried out in Birmingham in 1904. This was followed by many further examples in which he used mainly reduction, oxidation, and the Grignard reaction. He gave many examples of asymmetric induction. Incidental to his work were many resolutions of acids, amino-alcohols, bases, and esters, some of which proved very difficult experimentally.

McKenzie's quick appreciation of the value of the work of other chemists led him to be one of the first British scientists to use the Grignard reagents. The application of them in asymmetric syntheses has already been noted (see above). The preparation of (−)-benzoin from (−)-mandelamide opened a fruitful field and was followed by that of other acyloins on similar lines. The conversion of (−)-phenylchloroacetic acid into (+)-diphenylsuccinic acid is interesting by reason of the almost complete retention of optical activity. The reagent was also used for the preparation of the diethylamides of α-hydroxycarboxylic acids and of optically active and inactive glycols.

Among McKenzie's unclassified researches two may be mentioned. The isolation of pure, optically active amyl alcohol from fusel oil made a much-needed addition to the number of optically active alcohols available for stereochemical research. The examination of the resolution of ammonium racemate by moulds showed that, contrary to the then-prevalent idea both active components are attacked simultaneously but at different rates.

H. Wren.

WALTER COLLINGWOOD WILLIAMS.

1863—1951.

Walter Collingwood Williams died on April 5th, 1951, in his 89th year; by his death the chemical profession has lost probably the last of the original pioneers who " blazed the trail " of the Public Analyst.

He was apprenticed to one of the London Guilds and, after serving his full term, studied at London University, obtaining his B.Sc. degree with honours in chemistry and physics. He then attended Mason College, Birmingham, and was elected Associate of the College in 1884.

On leaving Birmingham he became an assistant to Dr. J. Campbell Brown and shortly afterwards was appointed, jointly with Dr. Brown, Public Analyst for Lancashire, Liverpool, and several boroughs. On the death of his chief in 1910 he became whole-time Public Analyst for Lancashire, a post which he held until his retirement in 1926.

He was elected a Fellow of the Society in 1885 and became a Fellow of the Institute of Chemistry in 1893.

In the early days of his career the post of Public Analyst had only recently been established. Very little attention had been given to the composition of foods or to the detection of adulteration. Hassall had published his classical researches on microscopy applied to food stuffs but no corresponding work had appeared relating to analytical investigations. Consequently in the Lancashire County Laboratory, as in other laboratories, research was carried out to obtain information regarding the composition of foods and the detection of adulteration, and to establish limits and standards. Williams threw himself whole-heartedly into this work; his enthusiasm was such that it stimulated the deep and permanent interest in those who served under him.

A vast amount of information was accumulated as the years passed but little or none of it was published with the exception, it is believed, of a paper on Jamaica rum. Had his policy been to make known the results of his work he would have occupied a much more prominent position than he did in the profession.

Williams had a very reserved temperament, and a sense of humour, though very seldom did evidence of it emerge in working hours. In this connection it should, in fairness, be mentioned, that at the period usually regarded as the prime of life his eyesight began to fail and it seems quite likely that this misfortune would emphasise a disposition that had always been a retiring one.

The chief recreation of his active life was mountaineering and he scaled many peaks on the continent and in Britain. He was very much attracted to all mechanical contrivances; microscopy claimed much of his spare time and he attained a wide and thorough knowledge of the subject. He was a devoted member of the Liverpool Microscopical Society.

N. HERON.