OBITUARY NOTICES.

JOHN WILLIAM BLAGDEN.

1876—1942.

Dr. J. W. Blagden died on November 28th at his home in Loughton, Essex, in his 67th year. He came from a scientific family, and was educated at Dulwich and Emmanuel College, and took an Honours degree in Natural Science in 1895. Proceeding to Würzberg, he worked under Hantzsch, obtained his Ph.D., and after a period as Senior Demonstrator in Electro-Chemistry at Darmstadt, entered industry with C. F. Bohringer und Söhne as Research Chemist and Departmental Manager. He worked on electrolytic oxidations and reductions and later became interested in the then new field of catalytic hydrogenations. In this, particularly in its applications to industry, he was one of the pioneer workers. The outbreak of war in 1914 put an end to his work in Germany. During the period of hostilities he was an internee at Ruhleben, where as the leader of a group he endeavoured to continue scientific work, an effort typical of a man who refused to be dismayed by difficulties. At the end of the war he returned to England and sought an opportunity to continue his work on catalysis. He joined Messrs. Howards and Sons, Ltd., in 1919 and undertook the organisation and direction of a newly formed Research Department. The range of new products manufactured by the firm during the last twenty years is a tribute to the energy and skill with which he pursued the task. In 1929 he was elected a Director of the Company.

He was a Fellow of the Chemical Society and of the Institute of Chemistry, and a Member of the Society of Chemical Industry. He served on a number of Committees, among which may be mentioned the Pharmacopœia Commission, the Essential Oils Committee of the Imperial Institute, Chemical Committees of the British Standards Institution, and the Patents Committee of the Association of British Chemical Manufacturers.

He had little desire or time for publication, and apart from a few relatively minor papers the record of his work exists in patents and in the technical achievements of the laboratory under his direction.

Blagden was always accessible to members of his staff, and devoted much of his time to their encouragement and welfare.

He felt that Industry owed a debt to the Universities, and was pleased to acknowledge this by both material and technical assistance whenever possible.

G. C. Clark.

ARTHUR HARDEN*

1865—1940.

Arthur Harden died on 17 June 1940 at his home at Bourne End.

Harden was born in Manchester on 12 October 1865. His father was Albert Tyas Harden, a Manchester business man, who had married Miss Eliza MacAlister, of Paisley. He was the only son, but there were several sisters, and the family was brought up in an austere nonconformist atmosphere, abjuring the theatre and regarding Christmas as a pagan festival. At the age of seven years he was sent to a private school kept by Dr. Ernest Adam in Victoria Park, Manchester, and four years later he went on to the Tettenhall College in Staffordshire, where he stayed until he was sixteen. In January 1882 he entered the Owen's College, Manchester, and studied chemistry under Professor Roscoe, then at the height of his fame as a teacher. In 1885 he graduated in the Victoria University with first-class honours in chemistry. A year later he was awarded the Dalton scholarship.

It was J. B. Cohen, to whose stimulating teaching Harden doubtless owed much, who suggested the subject of his first research, " The action of silicon tetrachloride on aromatic amide-compounds," and in the following year the results of this investigation were published in the *Transactions of the Chemical Society* (1886). From Manchester he proceeded to Erlangen, and under the direction of Otto Fischer prepared β-nitroso-naphthylamine and investigated its properties. Having been awarded the degree of Ph.D., he returned to Manchester and there became first junior and then senior lecturer and demonstrator under Professor H. B. Dixon, who had meantime succeeded Sir Henry Roscoe as professor of Chemistry. During part of this time Harden shared the laboratory teaching with Hartog (later Sir Philip), and for some years he lectured to the honours students on the history of chemistry, a subject in which he was greatly interested. This interest was shared by Roscoe: together they studied the note-books of Dalton and arrived at the conclusion that it was Dalton's investigation of the relations governing the diffusion of gases that led him to formulate his atomic principles. They published their views in 1897 in the *Philosophical Magazine* and in the *Zeitschrift für physikalische Chemie*, and afterwards in a book entitled *A new view of the genesis of Dalton's atomic theory*. Harden's interest in Dalton endured, and in 1915, with H. F. Coward, he communicated to the Manchester Literary and Philosophical Society a description with comments of some of the lecture sheets with which Dalton used to illustrate his lectures and which had recently been discovered in the rooms of the Society.

In 1895 Roscoe and Harden collaborated in writing a textbook to fulfil the needs of students for the higher

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South Kensington examination. In collaboration with F. C. Garrett, Harden also wrote a book on *Practical organic chemistry,* designed to supplement Perkin's *Organic chemistry,* and also undertook with Colman the work of revising and editing a new edition of Roscoe and Schorlemmer's *Treatise on inorganic chemistry.* All this literary activity served as valuable training for the editorial work which was to occupy so much of the time of his later life.

During these nine years in Manchester, Harden seems to have been chiefly interested in his teaching and literary work. He published only two papers based on experimental work; both appeared in the *Transactions of the Manchester Literary and Philosophical Society,* one with W. Haldane Gee on a new form of stereometer (in 1891) and the other on the composition of some iron and bronze implements which had been found by Professor Flinders Petrie in 1897. He began experiments on the combination of carbon monoxide and chlorine, with a view to studying the phenomenon of photo-chemical induction, a subject in which Dixon was especially interested: this work was carried out in collaboration with Dyson, but the results were not published until 1903, six years after Harden had left Manchester. It seems, therefore, that up to the time he left Manchester, at the age of thirty-two, Harden had not manifested an overpowering desire for scientific research. He had applied for the posts of Principal at the Wandsworth Technical Institute and of Inspector under the Science and Arts Department at South Kensington: fortunately both these applications were unsuccessful.

In 1897 Harden was appointed to succeed Joseph Lunt as chemist to the Jenner Institute of Preventive Medicine in London. The choice was made largely on the grounds that he had a wide knowledge of chemistry and had proved himself to be a successful teacher. At that time the institute provided instruction in bacteriology and chemistry for medical practitioners desiring to equip themselves to become medical Officers of Health. Harden was responsible for the chemical course which was mostly concerned with the analysis of water and foods.

After a few years, however, the London medical schools introduced special teaching for those wishing to qualify for a diploma in public health, so the classes at the Jenner Institute were discontinued and Harden was henceforth free to devote his whole time to research.

There were then two chemical departments at the institute (which had meantime changed its name to Lister Institute), one called Chemical was under Harden, the other Biochemical was presided over by Hedin, with Leathes second in command. In 1905 Hedin left and Leathes was shortly afterwards invited to occupy a chair of pathological chemistry at Toronto, so the two departments were fused and Harden was placed in charge. In 1912, in recognition of his outstanding work on bacterial chemistry and alcoholic fermentation, he was made Professor of Biochemistry in the University of London.

At the Jenner Institute Harden made his first contacts with biology. His senior colleague was Alan Macfadyen, who was in charge of the bacteriological department, and it was at the latter's suggestion that in 1898 he embarked upon an investigation of the fermentation of sugars by bacteria. The original object of this was to find diagnostic means for the differentiation of varieties of *Bacillus coli,* but Harden gave a wider scope to the research. He kept a carbon balance sheet by determining the amounts of the various products. Incidentally, he discovered several substances not known at that time to be formed by the bacterial decomposition of sugars. Several products of the fermentation of *B. coli* had been identified earlier, but Harden was the first to construct a picture of the breakdown process as a whole. His first paper on the action of *B. coli communis* and allied organisms on sugars appeared in 1899 and a more extensive account in 1901. In this he compared the results of the fermentation of glucose with that of other hexoses and pentoses and on mannitol and glycerol. He showed that acetic acid and ethyl alcohol were formed in equimolecular proportions and that the two terminal alcohol groups were the source of them. In 1905 he published similar observations upon the action of *B. lactis aerogenes.* With this organism the amount of acetic acid and alcohol formed was not equal. One-third of the glucose fermented could not at first be accounted for, and the deficit was found partly in the form of acetyl methylcarbinol and partly as the reduced form as butylene glycol. These two substances had not hitherto been known to be products of bacterial action on sugars. The former, he found, was the substance responsible for the colour reaction of Voges and Proskauer used as a diagnostic criterion by bacteriologists. Further papers on bacterial chemistry with Norris and with Penfold appeared in 1912.

Harden's work on bacterial chemistry did not attract as much attention at the time as its merit justified. The bacteriologists did not appreciate what it was about, and it was too far removed from the interests of all but a few chemists. It was, indeed, pioneer work and formed the basis on which many interesting researches into bacterial metabolism have subsequently been built.

Harden commenced to work on bacterial chemistry in 1897, and in 1900 he started his researches on alcoholic fermentation, in the course of which he made some notable discoveries which will remain associated with his name. These two lines of research proceeded simultaneously for some ten years, but for simplicity of description they are dealt with separately.

ALCOHOLIC FERMENTATION

Harden derived his interest in alcoholic fermentation also from his bacteriological colleague, Alan Macfadyen, who, like most microbiologists, was impressed with Buchner's discovery that the cell-free juice expressed from yeast would ferment sugar.

The belief that alcoholic fermentation required the operation of the intact living cell having been superseded, a new experimental method for its study had been found. The first crude preparations of zymase had, however, two drawbacks: (1) yeast juice produced a considerable amount of alcohol and CO_2 without the addition of sugar; (2) it rapidly lost its power to ferment. Harden's first researches were concerned with discovering the cause of these disturbing phenomena with a view to overcoming their hindrance to quantitative experimentation. Autofermentation he found to be due to the action of the enzyme upon the glycogen expressed from the yeast cells and that it ceased when this supply was exhausted. Deterioration in fermentative activity, he concluded, was brought about by destruction of the zymase by the proteolytic enzyme also present in the expressed juice, for by the time autolysis was advanced its power to ferment had disappeared.

It was whilst engaged on these investigations, neither of which had direct significance for the understanding of the chemistry of the transformation of sugar into alcohol and CO_2, that he made two fundamental discoveries. The first was that the enzyme zymase would not convert sugar into alcohol unless another substance which functioned as a co-ferment was present. The second was that the presence of phosphate was also necessary.

It is doubtful whether Harden would have made the advances he did had he not early abandoned the gravimetric measurement of CO_2 produced, which had been used by Buchner and others, and adopted a volumetric one. The simple method he substituted enabled him to make frequent determinations of the CO_2 evolved and thereby study the progress of the reaction at ten-minute intervals, if necessary, throughout the period of the experiment.

In his studies on alcoholic fermentation Harden was powerfully supported by a number of able pupils and collaborators which he had attracted to his laboratory. Notable amongst these were W. J. Young, now Professor of Biochemistry in the University of Melbourne; R. Robison, who succeeded him; Lord Henley; and Miss Macfarlane, who still carries on the good work at the Lister Institute. These collaborations with younger folk were happy and fertile. Harden's strong points as an investigator were his wide knowledge of chemistry and his capacity to analyse the results of an experiment dispassionately and define accurately what interpretations were justifiable. He was a superb critic but unduly suspicious of adventures into the realm of imagination.

THE CO-ENZYME

How Harden came to discover co-zymase and the rôle of phosphates in alcoholic fermentation makes an interesting story which indicates his measure as an investigator.

For some reason or another, which is not now material, he added boiled autolysed yeast juice to a mixture of zymase and sugar solution and found that the rate of fermentation was thereby greatly increased. At first he attributed this to some restraining influence on the proteolytic enzyme, always present with zymase, which he had previously found to be inhibited by horse serum and other proteins. This explanation had, however, to be put aside after appropriate experiments, and he was faced with the fact that yeast juice contained, in addition to zymase and a proteolytic enzyme, a substance stable to boiling which favourably influenced fermentation. Additional study of its properties showed that it was thermostable, dialysable through parchment paper, destroyed by incineration and precipitated by 75 per cent. alcohol.

Further than this he could not advance until some satisfactory method of separating the unknown substance from zymase was found. Dialysis was too slow, for meantime the zymase was being destroyed by the proteolytic enzyme.

The separation was ultimately achieved by employing a Martin gelatin filter, by means of which a separation could be effected in a few hours, the zymase remaining on the outside of the filter and the activating substance passing into the filtrate. Neither the redissolved residue nor the filtrate alone would ferment, but when the two were mixed fermentation occurred at about the original rate. For this necessary adjunct to fermentation by zymase the name co-ferment was suggested.

Harden did not discover more as to its nature beyond finding that it contained phosphoric acid in its make-up, nor as to what stage in the conversion of sugar to alcohol it was operative, but he did hazard the suggestion that as it contained phosphate it might be involved in the phosphorylation of the hexose, which he had also discovered to be an essential stage in the process and which will be dealt with immediately. The constitution of the co-ferment was ascertained by von Euler some years afterwards. He showed that it was a complex nucleotide containing adenine, nicotinic acid and rhibose, and proposed the name co-zymase for it.

THE ESSENTIAL RÔLE OF PHOSPHATES

Experiments with boiled yeast juice also led Harden to discover the necessity for phosphates in fermentation by zymase. As just mentioned, the co-ferment was destroyed by incineration, or could be precipitated by 75 per cent. alcohol, but the ash or the filtrate after precipitation still produced a temporary increase in the production of CO_2.

This result led to the trial of the addition of potassium phosphate. The result was startling. In fifteen minutes the rate of production of CO_2 had increased sevenfold. It then fell as rapidly to the original rate. It was much as if an acid had been added to a solution of bicarbonate, for the amount of CO_2 produced was equimolecular with the HPO_4 added.

This and the fact that it could be repeated, indicated that the phosphate had somehow become fixed. This was proved by showing that the phosphate was no longer precipitable by magnesia mixture. Harden and Young subsequently found that it had combined with the sugar to form a hexosediphosphate. This ester was subsequently isolated and identified by Young.

The study of the fermentation of mannose and fructose threw further light on the constitution of the hexosephosphate. Mannose was fermented as rapidly and fructose more rapidly than glucose. The rate of fermentation of all three sugars was accelerated by phosphate, but that of fructose was double that of glucose or mannose and it was much less rapidly inhibited by the further addition of phosphate. The hexosediphosphate prepared from these three sugars was identical and the quantitative relations were expressed by the same equations. It was suggested that the hexosephosphate was probably derived from the enolic form common to the three sugars, though the possibility that the two molecules of sugar were broken down into smaller groups and hexaphosphate resynthesized from these was considered possible.

As fermentation by the intact yeast cell proceeds at a uniform and enhanced rate compared with that by zymase, it was clear that the bound phosphate must be liberated as quickly as it was formed. Harden and Young soon discovered that yeast contained a phosphatase which hydrolysed hexosediphosphate, so presumably this accounted for its non-accumulation and they thought that this mechanism must be defective in the case of yeast juice and so account for the relatively slow rate of fermentation.

Experiments were therefore made in which phosphatase prepared from yeast was added to a zymase preparation in which fermentation had nearly ceased after the spurt occasioned by addition of phosphate. The addition of phosphatase caused the fermentation rate to increase much as if a new dose of phosphate had been added, but it could not be maintained, although the increased rate endured longer than when phosphate was added. The conditions obtaining in the living cell could not be completely imitated in zymase fermentation, as for some reason the added phosphatase lost its activity, but it could be done indirectly by the addition of arsenates—a result no one could have foreseen. As Harden said in his Nobel lecture, " this observation was the undeserved reward for thinking chemically about a biochemical problem, a dangerous thing to do." As in many chemical reactions arsenates behave like phosphates, out of curiosity he tried whether they could replace them in alcoholic fermentation. This did not occur. The addition did indeed increase the rate of fermentation, but the effect was not sudden and temporary as that of phosphate, but slower and more lasting. Arsenates behaved in an entirely different way, apparently by preventing the destruction of phosphatase.

Harden and Young suggested that their observations indicated that fermentation could be illustrated by two equations :

(1) $2C_6H_{12}O_6 + 2Na_2HPO_4 = C_6H_{10}O_4(PO_4Na_2)_2 + 2H_2O + 2CO_2 + 2C_2H_6O$;
(2) $C_6H_{10}O_4(PO_4Na_2)_2 + 2H_2O = C_6H_{12}O_6 + 2Na_2HPO_4$.

the first representing the evolution of CO_2 and production of alcohol and accumulation of phosphoric ester; the second the hydrolysis of the ester with liberation of a hexose and mineral phosphate.

In the presence of arsenate, equation (2) proceeds sufficiently rapidly to supply phosphate so that equation (1) proceeds with maximal velocity.

In 1914 Harden and Robison discovered that the diphosphate was not the only phosphate ester formed during fermentation, but that hexosemonophosphate was also present. The relative amount of these two phosphates varied from 80 per cent. of one or the other according to circumstances. Nevertheless the ratio of CO_2 evolved to PO_4 esterified remained constant and approximately unity. What were the conditions for the preferential formation of the mono- or diphosphate could not be discovered. Harden was convinced that complete reaction of some sort took place as the result of which two phosphate groups were introduced into certain sugar molecules—either into the same molecule or one each into two different molecules—and this induced the decomposition of another molecule of the carbohydrate. Robison and he showed that the monophosphate reacted with a further quantity of phosphate and was accompanied by an increased production of CO_2.

Harden recognized that the only quantitative relation that his experiments had established was that during the course of fermentation by yeast juice, or by dried yeast, for every one molecule of phosphate esterified approximately one molecule of CO_2 was evolved.

This view and its expression in the form of the equations (1) and (2) above truthfully expressed the beginning and the end of the reactions and the final result. The intermediate stages, however, still remained obscure until Meyerhof and his colleagues established that the monophosphate was the first product, and that hexosediphosphate was formed by the further phosphorylation of the monophosphate, which was then converted into two molecules of triosephosphate, that the course of the breakdown began to be clearer.

Henceforth, with the exception of four years during the late war, most of Harden's research activities were devoted to attempts to elucidate the reactions involved in fermentation and the rôles played by zymase, cozymase and phosphates respectively. It was a period of controversy, with experiment and counter-experiment, and it is difficult to make a connected story of Harden's contributions, for the significance of individual experiments is not easily apparent.

Buchner's suggestion that lactic acid was an intermediate in sugar fermentation was rejected by Harden, a view in which Buchner eventually concurred, though unfortunately not before it had been widely accepted by biologists. Iwanoff claimed to have isolated a triosephosphate giving an osazone (m. p. 128°) similar to one prepared by Lebedeff from the oxidation products of glycerol. According to Iwanoff the formation of hexosephosphate preceded the alcoholic fermentation and the amount of fermentation should be found proportional to the amount of hexosephosphate decomposed. Harden did not at first accept this view, but the existence of Iwanoff's triosephosphoric acid was confirmed in 1907 by his colleague Young, who isolated it as a lead salt.

No attempt seems, however, to have been made by Harden to introduce the triosephosphate into his equations. It was shown by Macfarlane, working in Harden's laboratory, that an autolysed solution of dried yeast which was incapable of fermenting glucose even after the addition of the co-enzyme could decompose hexosediphosphate, producing inorganic phosphate and CO_2. The existence of a definite phosphatase acting on the hexosediphosphate was therefore established. When co-enzyme and arsenate were added the decomposition of the hexosediphosphate was extremely rapid, and CO_2 and inorganic phosphate appeared as final products of the decomposition. It was the breakdown of the hexosediphosphate that was stimulated by the presence of arsenate.

Eighty per cent. of the great fall in fermentative activity which occurred when fresh yeast was converted into yeast juice was found to occur during the process of grinding, and it was during the same period that the yeast acquired the power of responding to phosphates. It was therefore concluded that the phosphatase was destroyed.

The nature of the enzymes in yeast and their method of action was investigated by Harden and his colleagues in a long series of researches.

He confirmed Neuberg's discovery of the existence of the enzyme carboxylase in dried yeast, which split pyruvic acid into CO_2 and acetaldehyde and showed that as this reaction took place after the co-enzyme had been completely washed away, it was independent of the presence of the co-enzyme. The reducing power of zymin or dried yeast on the other hand was removed by washing, but could be restored by the addition of the boiled washings. Certain aldehyes also restored the reducing power and therefore had the property of acting as oxygen acceptors. Similar experiments carried out with washed rabbit's muscle showed that here the addition of either lactic acid or acetaldehyde restored the reducing power. Evidence was also obtained of the existence of a peroxidase in fresh yeast. The peroxidase activity was lost on drying for seventeen hours at 37° C. but was again detected after the dried yeast had been washed. The catalase activity was not affected by washing, whereas invertase, but not maltase, was removed by washing the dried yeast. Harden also showed that the presence of inorganic salts exercised a marked influence on the autofermentation of yeast; all dissolved substances which plasmolysed the yeast cell caused also a large increase in the rate of autofermentation. Washed zymin in the presence of a suitable concentration of sodium phosphate was activated by potassium pyruvate, but not by acetaldehyde; if, however, the sodium phosphate were replaced by the potassium or ammonium salt, acetaldehyde also acted as an activator. There was therefore a specific salt effect, the sodium ion acting differently to the potassium or ammonium ion. On the other hand, when the fermentation of fructose or glucose by dried yeast preparations was examined it was found to be equally depressed by the addition of sodium or potassium chloride and the effect of the sulphates was somewhat greater. This action was shown to affect the rate of action of the hexaphosphatase but not that of the carboxylase. Potassium phosphate was also shown to produce a depressing effect, but in this case, unlike that of the sulphate, the depressing effect could be largely counteracted by the addition of acetaldehyde to the solution.

APPLICATION OF HARDEN'S DISCOVERIES TO BACTERIAL METABOLISM AND ANIMAL PHYSIOLOGY

After Harden's discovery of the co-enzyme and of the important part played by phosphates and phosphoric esters in alcoholic fermentation, it was soon discovered by various workers that phosphorylation provided the clue to many other biological phenomena.

Harden's earlier work on bacterial metabolism was done before his studies of fermentation by yeast had revealed the importance of phosphorylation as a factor in the latter. He did not himself undertake experiments to decide whether it would prove of equal importance in the former. During recent years, however, the work of many investigators has shown that this is actually the case. During glycolysis under the influence of *Bacillus coli*, for instance, the bacterium which had been Harden's chief concern, the main stages of breakdown are undergone by phosphorylated molecules. In brief, the following sequence occurs: Hexosediphosphate yields phosphoglyceraldehyde. By dismutation this yields 1-glycerolphosphate and phosphoglyceric acid. Of these two products the former breaks down into ethyl alcohol and free phosphates, while the latter yields phosphopyruvic acid. In aerobic conditions this last product breaks down into free phosphate, acetic acid and CO_2; while anaerobically formic acid takes the place of CO_2. The liberated inorganic phosphoric acid becomes available for the further formation of the original hexosephosphate.

An astonishing degree of similarity was also found to exist between almost every detail of the production of lactic acid by the muscle enyzmes and of alcohol by the yeast enzymes, which extended to the identity of the phosphoric esters concerned, the accumulation of ester under similar conditions and even to the effect of arsenates on the process.

In an aqueous extract of muscle glycolysis proceeds, but neither glycogen nor glucose molecules suffer change until they have become associated with phosphoric acid as its esters. The various simpler molecules which represent intermediate stages in the sequence of anaerobic reactions which ultimately liberate the available energy of the original carbohydrate molecules also undergo esterification or suffer substitution by the phosphoryl radicle. Of fundamental importance in maintaining the sequence of events is the circumstance that the phosphoryl radicle is readily transferable from one molecule to another, from a donator of phosphate to a receptor. Such transference leads to the coupling of reactions, and in particular cases may result in the actual transference of energy from exothermic to endothermic events. The study of these phenomena gained much in interest when it was shown (in the School of Parnas in Lwow; in Cambridge by D. M. Needham and van Heyningen, and by Meyerhof and collaborators) that the progress of the reactions depends in general on the presence of adenylic acid in muscle. It has been shown, for instance, that the events which yield the lactic acid of anaerobic glycolysis involve an oxido-reduction reaction strongly exothermic in character. It comprises an oxidation of glyceric aldehyde and a simultaneous reduction of pyruvic acid. In the absence of either inorganic phosphate or adenylic acid, however, this reaction does not occur. In their presence it actively proceeds, yielding the energy for a strongly endothermic reaction, namely, the esterification of adenylic acid to adenose pyrophosphate. This latter is a compound with high free energy content, exerting indispensable functions both as a donator and receptor of the phosphoryl ion.* On hydrolysis its energy is liberated and it is indeed legitimate to speak of the energy of phosphate bonds. It would seem that the myosin of the muscle fibres itself catalyses the dephosphorylation of this pyrophosphate. It is likely, therefore, that a local breakdown in the fibres yields, or contributes to, the energy necessary for muscular contraction. The pyrophosphate structure is then reconstituted by transference of phosphoryl from yet another muscle constituent, namely creatin phosphate, which may be looked upon as a phosphate accumulator.

It is of interest to find that another aspect of Harden's work, namely, his demonstration of the effect of arsenate, has greatly assisted towards an understanding of the mechanism of the reactions just described. At the same time, the muscle studies have more fully explained the effect of arsenic on alcoholic fermentation.

This brief account omits many details now known concerning the events in muscle, nothing, for instance, being said about the enzymes which catalyse the reactions. It should make clear, however, the remarkable lines on which the influence of phosphates is exerted. Recognition of the significance of Harden's discoveries constituted a turning point in the history of muscle chemistry.

Robison's significant observations on ossification were also a direct outcome of his association with Harden in work on fermentation. The question why calcium and phosphorus should be normally deposited in cartilage that was about to ossify and only pathologically elsewhere remained unanswered. It occurred to Robison that there must exist in ossifying cartilage some conditions producing supersaturation of calcium and phosphate ions, and that one way in which this might occur would be by the decomposition locally of phosphoric esters in the blood supplied, supposing the tissue contained phosphatase. On examination it was found that cartilage about to ossify did indeed contain a phosphatase, whereas it was absent from the cartilages of the patella and of the trachea which do not undergo ossification.

When war broke out in 1914, the Lister Institute soon became depleted of most of its male staff and research students, while those who remained concerned themselves with problems having some relationship to our state of belligerency. Harden was left in charge of the institute during the absence of the director on military service. Wanting to devote himself to some subject which would contribute to the war effort, he abandoned his researches on alcoholic fermentation for five years and investigated two of the then known accessory food factors or vitamins, lack of which there was good reason to believe was responsible for the diseases beri-beri and scurvy respectively. Both of these diseases had occurred amongst our troops at outposts in Asia and Africa, where, either from difficulty of transport or from being beleaguered, they had to subsist on a restricted diet. The study of accessory food factors had assumed military importance and the exploration of means to effectively supplement rations had become a matter of some urgency. These investigations were not confined to the application of existing knowledge, but involved work of a fundamental character as the chemical composition of the two factors was unknown and their properties but little known. In carrying them out, Harden had valuable assistance from S. S. Zilva, then a research student in his department.

They proved that neither 2-hydroxypyridine nor adenine was the active agent which cured beri-beri as had been stated. The two water-soluble factors were differentiated by the use of fuller's-earth, which absorbed the anti-neuritic but not the antiscorbutic factor. The former was shown to be essential for the growth of frogs. The fruit-fly *Drosophila* was found to need the antineuritic but not the antiscorbutic. The biological synthesis of the antineuritic by yeast was established.

Holst's experiments showing that scurvy was a dietary disease due to a deficiency of a specific substance were confirmed, and a step towards the separation of this principle was achieved by removal of the organic acids, carbohydrates and protein from lemon juice and the production of a residue of much increased potency. In collaboration with Dr. Still, the superiority of this concentrated product in the treatment of infantile scurvy was demonstrated.

The susceptibility of the antiscorbutic principle to adverse influences was studied and its particular sensitivity to alkalies discovered. The effect of heating and storage at different temperatures on the potency of fruit juices was investigated and results of immediate practical importance obtained.

Scurvy was produced in monkeys by a scorbutic diet and the relative antiscorbutic requirements of this animal ascertained. Rats, on the other hand, did not develop scurvy.

As, in older days, fresh ale had a reputation for antiscorbutic properties, and yeast being one of the richest sources of the antineuritic principle, stout, ale and fined beer were tested, but both principles were found lacking in all of them.

Although research on nutrition had not been Harden's métier, he adapted himself to work in this new field with conspicuous success, and the results achieved make a goodly contribution to the early development of our knowledge of accessory food factors. Incidentally, it led to his acquiring a wide knowledge of the subject, which was used to good effect in editing the three editions of *Present knowledge of accessory food factors*, published by the Medical Research Council in 1919, 1924 and 1932.

Recognition of the importance of Harden's researches came from many quarters. In 1909 he was elected a

Fellow of the Royal Society, and in 1935 was awarded the Davy Medal by the Society. He served on its council from 1921 to 1923. In 1929 he shared the Nobel prize for chemistry with von Euler. The Universities of Manchester, Liverpool and Athens conferred honorary degrees upon him, and the Kaiserlich Leopold Deutsche Akadamie der Naturforscher of Halle elected him to its membership. In 1936 he received the honour of knighthood.

An account of Harden's scientific career would be incomplete without some reference to his teaching ability and his literary activities. In the early days at Manchester his powers as a teacher were recognized. At the Lister Institute he had little opportunity to exercise this gift in which he found pleasure, but for many years he devoted one evening a week to a class in microbiology at the Sir John Cass Institute, and for a while gave a course of evening lectures on biochemistry at the Chelsea Polytechnic. In both he took the greatest pains and interest.

Literary work took up a good deal of his time. Beside the very onerous work of editing the *Biochemical Journal*, he wrote the article on " Fermentation " for Thorpe's *Dictionary of chemistry* and the section on yeast enzymes for Oppenheimer-Pincussen's *Die Fermente und ihre Wirkungen* and the section on alcoholic fermentation, " The early stages of fermentation in the yeast cell," for *Die Ergebnisse der Enzyme Forschung*, and he was the author of the monograph on Alcoholic Fermentation in the Longmans series of *Biochemical monographs*, of which four editions have already appeared.

Harden's outstanding qualities as an investigator were clarity of mind, precision of observation and a capacity to analyse dispassionately the results of an experiment and define their significance. He mistrusted the use of his imagination beyond a few paces in advance of the facts. Had he exercised less restraint, he might have gone further; as it was, he had little to withdraw.

His personal relations with his fellow-men were controlled by an uncommon reserve. His attitude to most was that of a benevolent neutral. Few reached intimacy with him, but those who did penetrate his protective covering found in him a lovable and staunch friend.

He was generally cheerful, but never exuberant and suspicious of exuberance in others. He had a dry humour and was capable of unexpected flashes of wit. It was not his habit to offer his opinions unasked, but his advice and help were freely given if called for.

He had a very equable temperament and said that he had never known great elation or great depression. The uncommon control he exercised over his emotions was perhaps attributable in part to the severe puritanical discipline of his early life. Whatever the cause, his judgment was little influenced by them, so that he was pre-eminently a fair man. He would have made a great judge.

In 1890 he married Georgina Bridge, of Christchurch, New Zealand. His wife died in 1928; they had no children.

In 1930 he retired from his professorship at the Lister Institute, but continued to come every day to his laboratory, carrying on experimental work and correcting proofs for the *Biochemical Journal* until a year or two before his death. Towards the end of his life he suffered from a progressive nervous disease from which release came before it had become too irksome and while he still enjoyed his garden, his books and his interest in science.

F. G. HOPKINS.
C. J. MARTIN.

ALFRED HUTCHINSON.

1866—1938.

ALFRED HUTCHINSON, who died on August 19th, 1938, at the age of 72, was a native of Middlesbrough, and throughout his life was associated with the iron and steel industry of that district. His father, Mr. Thomas C. Hutchinson, managing director of the Skinningrove Iron Co. Ltd., was well known as an original and enterprising industrialist, who was responsible for many innovations in iron and steel plant. His son passed through the local High School and at the age of 15 went to Leys School, Cambridge. He took a London B.Sc. degree, intending to enter the family business, but becoming interested in biology and medicine, he returned to Cambridge, and gained a Major Scholarship at Trinity College. He obtained first class honours in the Natural Science Tripos and took a post as junior science master in his old school. With the head master, Dr. C. W. Kimmins, he built up a Science VI form, and among their pupils were Sir Joseph Barcroft and Sir Henry Dale. In 1894 he left Cambridge and entered the Skinningrove works, being first secretary, then blast-furnace manager, and on his father's death managing director and later chairman. He was concerned in a number of technical improvements, and contributed papers to the Iron and Steel Institute on questions relating to metallurgical fuels. In that Institute he took an active part, and held the Presidency for the year 1937—38. He became a Fellow of the Chemical Society in 1894. He was keenly interested in all questions relating to fuel, iron and steel, and his wide scientific culture stood him in good stead. He was greatly respected in the industry, and also in the county and municipal life of the North Riding, with which he was connected for so long.

C. H. DESCH.

GRACE CUMMING LEITCH.

1889—1942.

Grace Cumming Leitch was born at Cupar, Fife, on July 14th, 1889, and died there on March 12th, 1942. From Bell Baxter School she proceeded to the University of St. Andrews, graduating M.A. in 1912 with honours in mathematics and natural philosophy; B.Sc. in 1913; and Ph.D. in chemistry in 1919. She was Assistant at St. Andrews and later became Lecturer in Chemistry (1920—1942) at King's College, Newcastle-upon-Tyne, University of Durham. From 1926 she served also as Sub-Warden of Easton Hall of Residence for women students. Her published researches in this *Journal* include papers with W. N. Haworth on lactose and melibiose (1918), maltose (1919), the biose of amygdalin (1922), and one paper on melezitose and turanose was published independently (1927); also papers with G. R. Clemo and others on lupin alkaloids (1928), lupanine (1931), phenyl- and pyridyl-glyoxalines (1938). Among scientific workers she had a wide acquaintance, fostered by her regular attendance at the annual British Association meetings. Few could have failed to appreciate her gaiety of spirit, warm enthusiasm and loyalty, her capacity for friendship, and her vigorous personality; for it was these qualities which commended her to her students and colleagues, by whom she will be greatly missed.

W. N. Haworth.

HERBERT MARSDEN.

1883—1943.

Herbert Marsden died at The Lodge, Lockington, near Derby, on March 23rd, 1943, at the age of 60.

He was born at Church, Lancashire, passed through the Manchester Grammar School, and then went on to the Victoria University, Manchester. After having there taken an Honours degree in chemistry in 1905, he entered University College, Nottingham, in order to be trained as a research chemist. It was there that the writer made his acquaintance, and, after a very close association during two years, learnt to appreciate and admire not only his exceptional ability but also his personal qualities. His skilful manipulation and particular aptitude for research work were so notable that at the end of his first session the Council of the College awarded him a research scholarship, during the tenure of which he studied certain organic derivatives of silicon; a record of the results of his work was published in the *Transactions* for 1908 (p. 198) shortly after he had become a Fellow of the Society.

With strangers Marsden was quiet and rather reserved, but in the company of friends and fellow students he was genial and expansive, showing a lively interest in their affairs and, in fact, in all matters concerning the life of the College; when he left Nottingham in 1907 to become chemist to Messrs. E. Packard & Co., Ipswich, he had gained the respect and good wishes of all who had known him.

In 1918 he became chief chemist to Messrs. Genatosan Ltd., manufacturing chemists, a post which he held until his retirement in 1938.

Marsden had many interests apart from those of his profession: he was a man of deep religious feeling and during the last 30 years of his life did a great deal of voluntary work for the church as a lay reader. He was an accomplished pianist, an authority on ecclesiastical architecture (of which he had a collection of photographs, many his own work) and a keen and successful gardener.

He leaves a widow and one (married) daughter.

F. S. Kipping.

JOSEPH WILLIAM MELLOR.*

1869—1938.

With the passing of Joseph William Mellor on May 24 science lost an outstanding worker. The clay industries of this country lost a great leader, a pioneer in clay technology, appreciated alike for his high endeavour, achievement, and astuteness.

Mellor was born at Huddersfield in 1869. When ten years old he was taken by his parents to New Zealand. During his youth he worked in a boot factory and took classes in the evenings at the Dunedin Technical School. At twenty-three he matriculated and a year later entered the University of Otago. After graduating and serving as a science lecturer at an agricultural college he was awarded an 1851 Exhibition which took him to the University of Manchester in 1899.

At Owens College, Mellor came under the influence of W. H. Perkin, jr., and H. B. Dixon. It is characteristic of his versatility that during this period at Manchester, from 1899 to 1904, he interested himself in problems of both inorganic and organic chemistry. Perkin suggested that he should synthesise and examine the α-alkyl derivatives of glutaric, adipic, and pimelic acids. His paper (*J. Chem. Soc.*, 1901, **79**, 1901) describes these syntheses and also records the dissociation constants of these acids. It was, however, the researches into the combination of hydrogen and chlorine, suggested by H. B. Dixon, which chiefly occupied his attention during his stay at Manchester. Prior to 1900, the union of these two gases had been studied by

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J. W. Draper, R. Bunsen and H. E. Roscoe, and E. Pringsheim. With his usual thoroughness, Mellor began his work by testing the conclusions of these workers. In Part 1 (*Proc. Chem. Soc.*, 1900, **16**, 221) he demonstrated the presence of oxygen as an impurity when hydrogen and chlorine are prepared by electrolysis. In Parts 2 and 3 (*J. Chem. Soc.*, 1901, **79**, 216) investigations on the solubility of chlorine in solutions of hydrochloric acid are recorded. With W. R. Anderson, he studied the Draper effect (*J. Chem. Soc.*, 1902, **81**, 414). The catalytic effect of water vapour on the reaction between the two gases had been investigated by H. B. Baker, who found that the dried, mixed gases only combined very slowly when exposed to sunlight. Baker's work was confirmed by Mellor, working in collaboration with E. J. Russell (*J. Chem. Soc.*, 1902, **81**, 1272). In Part 6 (*J. Chem. Soc.*, 1902, **81**, 1292) Mellor considered the period of induction associated with the combination of the gases. Previously this period had been adequately demonstrated by R. Bunsen and H. E. Roscoe. It had been explained as being due to the formation of an intermediate compound and its subsequent decomposition to give hydrochloric acid. E. Pringsheim had postulated a mechanism of the reaction based on the formation of Cl_2O as the intermediate compound. Mellor tested this hypothesis, found it untenable, and proceeded to indicate a mechanism based upon the formation of another intermediate compound. His later researches on this subject (*Proc. Chem. Soc.*, 1904, **20**, 53, 140, 196) were concerned with the effect of temperature on the period of induction and the activity acquired by chlorine on exposing this gas to light. By leading the electrolytic gases *via* separate tubes into the insolation vessel of the actinometer and exposing the chlorine on its way (*a*) to acetylene light, or (*b*) to the silent electric discharge, or (*c*) to the heat of a bunsen flame, he found that the period of induction was considerably reduced. Mellor's other publications during this period included a note on the filling of Bunsen's ice calorimeter (*J. phys. Chem.*, 1900, **4**, 135); a method of estimating cyanides and cyanates (*Z. anal. Chem.*, 1901, **40**, 17); and a paper (with L. Bradshaw) on the kinetics of sugar inversion (*Z. phys. Chem.*, 1904, **48**, 353).

On leaving Manchester, Mellor went to North Staffordshire, and, after a short period as science master at Newcastle (Staffs) High School, he began his long association with the ceramic industries on his appointment as lecturer in pottery manufacture in Stoke-on-Trent. He formed a great friendship with Bernard Moore, the eminent potter, whose collaboration over a period of thirty years he valued very highly. Mellor wrote more than a hundred papers on ceramics, published in the Transactions of the Ceramic Society, the first appearing in 1904; the last he completed two months before his death. These investigations covered a very wide field and included the plasticity of clays; the specific heat of firebricks at high temperatures; the action of heat on refractory materials; the fine grinding of ceramic materials; the constitution of the clay molecule; and the crazing, peeling, and durability of glazes. His early study of the constitution of the clay molecule led to a consideration of the effect of heat on clays. For this work he received a grant from the Royal Society. Presenting the paper reporting this work (*Trans. Eng. Ceram. Soc.*, 1911, **10**, 94) to the Ceramic Society, he wrote: " Perhaps some apology is needed for presenting a paper so purely chemical to our Society. But clay is the lifeblood of pottery, and it is difficult to live with clay day after day without trying to form some idea of its nature and character. To-day we may not know enough to see the practical bearing of this work but who dare predict what we shall see to-morrow? ". In a footnote he also wrote: " Mr. Bernard Moore kindly looked through the proofs and then drew our attention to an important practical bearing of our work on the industry." Actually, the results of this and other similar investigations form the basis of our modern conception of the firing of clay wares. Mellor was always intensely interested in glazes but left the publication of some of his important work on this aspect of ceramics until towards the end of his life. His papers on " The Crazing and Peeling of Glazes " and " The Durability of Pottery Frits, Glazes, Glasses, and Enamels in Service " appeared in 1935 and gained world-wide appreciation. Mellor's ceramic work reveals a freshness of experience and intimate contact with all he describes. His keen sense of analogy, his wit, and his lucid expression adorn his many writings.

As a teacher of ceramics, Mellor gained considerable reputation. In this capacity he rendered great service to the staple industry of Stoke-on-Trent. Starting under great difficulties, he saw the realisation of a major objective in the building of the North Staffordshire Technical College in 1914. Here he carried out his duties as Principal of the Pottery Department until his retirement in 1934. His own early struggles made him very appreciative of the difficulties of his evening students. Indeed, his humanity was the foundation of his success as a teacher.

He became associated with the work of the Ceramic Society about three years after its formation, becoming honorary secretary in 1905, a position he held until his death. He raised the status of the Society from a local association to that of an international institution. He extended its field to include refractory materials and clay building materials as well as pottery. The Society's present eminence is a lasting testimony to his high endeavour.

There is obviously a close relationship between certain problems of the pottery industry and some of the difficulties associated with firebrick manufacture. Clay is the basic material of both industries. Mellor realised that practically every industry employing high temperatures in manufacturing processes is limited in scope or in efficiency by the durability of refractory materials. He considered it his duty to make contact with both the manufacturers and users of refractory materials, and, in 1909, due in large measure to his initiative, the Refractories Committee of the Institution of Gas Engineers was formed. This was a pioneer association for the prosecution of research into the manufacture, properties, and durability of refractory materials. Its considerable development was an important factor in the establishment of the British Refractories Research

Association, in 1919, under the aegis of the Department of Scientific and Industrial Research. Mellor was appointed the first director of research of the Association, a position he held until 1937. He enlisted and retained the support of the manufacturers and users of refractory materials, carefully fostered the programme of research of the Association, and founded the Mellor Laboratories, the present headquarters. It is recognised that, in this work, he rendered a conspicuous service to his country.

It is no easy matter to assess, at short range, the work of any man with whom one has been closely associated for many years. In spite of this, it is clearly true to say that Mellor will be remembered for many years by reason of his monumental work, *A Comprehensive Treatise on Theoretical and Inorganic Chemistry*, in sixteen volumes, which he completed in 1937, after twenty years of courageous effort. He often said that, when writing the early volumes, he did not appreciate the extent of his task. It was in keeping with his character that having started this work he could not be deterred from completing it. As each volume appeared, he received unstinted, well-merited praise for this great service to his fellow scientists. To his few intimate associates, the completion of these volumes is a source of complete bewilderment. They know of his perfect indexing system, that he wrote every word and every reference, and that during the writing of the last four volumes he was a very sick man.

In 1901, while working in Manchester, Mellor conceived the idea of writing his first book, *Higher Mathematics for Students of Chemistry and Physics*. This ambitious work was the result of certain difficulties he experienced as a student endeavouring to follow the many developments in chemistry. The book had marked success, running into four editions and being reprinted in 1926. He often confessed that he obtained great pleasure from the writing of *Chemical Statics and Dynamics*, which appeared in 1904. His *Treatise on Quantitative Inorganic Chemistry*, which first appeared in 1912, is a recognised authoritative work on silicate analysis. Finally, his exceedingly popular *Modern Inorganic Chemistry*, a book of unique individuality, had a remarkable vogue in the whole of the English-speaking world. He certainly combined great scientific attainments with a singular literary ability. His work was recognised by many bodies. A number of foreign societies, particularly including the American Ceramic Society, made him an honorary member. He was elected a fellow of the Royal Society in 1927. In the Coronation Honours of 1937 he received the C.B.E.

Mellor had a very happy life. He looked forward to his work and to his leisure. As a youth, endowed with considerable physical strength, he enjoyed a good reputation as a swimmer. In later life, he played an enthusiastic game of bowls. He was a highly accomplished chess player. His sense of humour, combined with his ability as a cartoonist, delighted his many friends. He had a vivid appreciation of loyalty and friendship. To those who knew him, his supreme loyalty was, indeed, his greatest attribute.

A. T. GREEN.

COLIN RICHARD MORRISON-JONES.

1914—1942.

COLIN RICHARD MORRISON-JONES was killed in action in the Middle East in July, 1942, in his twenty-ninth year.

He was born on August 3rd, 1914, and educated at Merton Court, Sidcup, Cranleigh School, and the Royal College of Science. He graduated with Honours in Chemistry in 1935, and gained the A.R.C.S. the same year; afterwards he entered the research school of Professor J. F. Thorpe in Organic Chemistry. In the research laboratory he soon found his feet and became greatly interested in high-vacuum distillation processes, which he applied to the isolation of the individual polymers contained in thermally-treated vegetable oil esters; ultimately he shared in demonstrating the manner of thermal polymerisation characteristic of a conjugated diene ester, for which work he was awarded the degree of Ph.D.

In 1937 he became research assistant to the Rubber Growers' Association, and in this capacity did fruitful work in investigating the chemical reactivity of rubber. A year later he joined the research staff of the Anglo-Iranian Oil Company. Early in 1939 he became a member of the London Volunteer Fire Brigade and at the outbreak of war was called up for full-time service with this body. His work as a qualified fireman, however, was soon interrupted by a more urgent demand for his services as a chemist; fire-fighting then became a part-time occupation. In the stirring days of the early autumn of 1940 neither chemistry nor fire-fighting could hold him any longer, and after repeated applications he succeeded in getting released for service with the Royal Air Force. He trained as a fighter pilot in England and Canada and became in turn Sergeant-Pilot and Pilot Officer. After some service with a fighter squadron in Great Britain he was transferred abroad, arriving in time to fly a Hurricane in the defence of Malta during the great German attack on the island in the autumn of 1941. The next year he joined a fighter squadron in Libya, where he took part in the withdrawal to El Alamein. On July 24th, 1942, he was reported missing, and was later found to have been killed in action. He rests at El Dab'a.

Morrison-Jones hid high ability and a courageous spirit behind a shy and unassuming manner. Only on long acquaintance did the strength of purpose behind his quiet friendliness become apparent. His death came before he had reached the height of his powers, but not before he had been able to render notable and most gallant service to his country.

E. H. FARMER.