and founded, in 1784, a lying-in hospital in which about 100 women were delivered annually.

Caesarean section in the eighteenth century was almost always fatal to the mother. In Ireland it had once succeeded, and then it was performed by an ignorant midwife, Mary Donally, in 1738-39; in England the first successful operation was performed by Barlow of Bolton in 1793, and in that case the child did not survive. The operation was stigmatized by Ould as a "detestable, barbarous, illegal piece of inhumanity." Although Smellie and Burton in the middle of the century, and Hamilton and Denman at the end, had accepted the operation for cases of extreme pelvic contraction, Osborn denied that either Caesarean section or symphyseotomy was ever a justifiable operation. He described cases of the severest degree of pelvic contraction in which he had been able to deliver by means of craniotomy, and, recognizing that the recovery of the mother depended on its being performed before she became exhausted, he extended the indications to cases which perhaps might have been delivered by forceps, and thereby attracted a good deal of censure, especially from foreign obstetricians, as the enthusiastic advocate of mutilating operations. In favour of Osborn it must be remembered that Caesarean section and symphyseotomy were at that time almost uniformly fatal, that British obstetricians have always regarded the child's life as less valuable than the mother's, and that fatal results to the mother from craniotomy depend almost entirely on its being performed too late. William Osborn, a friend and fellow lecturer of Denman, was born in London in 1736. In 1770 he joined Denman in founding a school of midwifery, and became one of the most successful teachers, more than twelve hundred practitioners of midwifery having attended his lectures.

For the performance of craniotomy either a guarded knife or scissors was employed, of which Smellie's scissors-perforator was the most practical. In the extraction of the child's head after perforation the crochet was mostly used—at first the straight instrument, afterwards the curved crochet, and finally (by Smellie) the double crochet. Opinions differed as to whether the instrument should be fixed inside or outside the skull. The forceps were also used for extracting the head (Smellie), or the forceps with a crochet at the end of the blade (Pugh).

Haemorrhages and Convulsions.

The haemorrhages most frequently recorded at this period were of the ante-partum variety, due to separation of the placenta either normally situated or praevia. Giffard was the first British author to point out the occurrence of true placenta praevia, as distinguished from prolapse of the organ. The treatment was sometimes rupture of the membranes, but usually podalic version. Post-partum haemorrhage was treated mostly by sedatives and tonics; but sometimes by local styptics, the disadvantages of which were recognized. Cold applications were also employed. There is no record of the employment of manual compression of the uterus. Several cases of haemorrhage due to inversion of the uterus are described, in some of which recovery followed the reduction of the inversion. A few cases of rupture of the uterus are mentioned; one of these is illustrated by Denman in a fine plate.

Convulsions were treated by bleeding, blistering, opiates (extract. or tinct. thebaic.), hot baths, and clysters. The temporal artery or jugular vein was often recommended as the vessel to be opened.

Ectopic Gestation and Hydatidiform Mole.

Interesting cases of these conditions were published by Giffard, with illustrations. The ovum of the ectopic gestation was passed by the rectum, to which the sac adhered. The case of hydatidiform mole terminated fatally a year after the delivery, a tumour being found in the uterus, which was thought to be the placenta, but was probably a chorion-epithelioma.

Summary Review of the Period.

It may be said that during the one hundred and fifty years after Harvey published his *De Generatione Animalium* a great advance was made in the science and

art of midwifery. This was chiefly due to the introduction of male practitioners, many of whom were men of learning and devoted to anatomy, the groundwork of obstetrics. The institution of lying-in hospitals by these male practitioners had an important influence in promoting teaching and research. The general introduction of the use of the forceps placed in their hands means, previously unknown, of delivering women, and by its results gradually overcame the opposition of the midwives, surgeons, and physicians to the new class of men-midwives. The action of the College of Physicians in instituting a special diploma of "Licentiate in Midwifery" was not without influence in improving the status of those practising midwifery, although it ceased to be granted in the year 1800.

The characteristic of British midwifery at this period was conservatism. Although by some practitioners carried to excess, it led to laudable attempts, exclusively British, to avoid the operations of craniotomy which sacrificed the child, and of Caesarean section and symphyseotomy which so often proved fatal to the mother.

The forceps were sometimes used unnecessarily then, as now; but the abuse of operative methods of delivery is much greater at the present time, and no better corrective of that abuse could be prescribed than a study of the careful records of the British obstetricians of the seventeenth and eighteenth centuries, showing the resources of that "perfect operatrix" Nature in effecting delivery.

CHEMICAL CHANGES ACCOMPANYING MUSCULAR ACTIVITY.*

BY

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As the subject open for discussion deals with the chemical changes associated with muscular activity it is necessary in the first place to consider the nature of the constituents which probably play a part in the energy changes associated with activity. These chemical changes are mainly concerned with the transformations of glycogen. As the transformations are brought about by the action of enzymes within the muscle, there must at all times be present in muscle evidence of enzymatic changes having been in progress, and thus it is to be expected that the products of ferment action should be present in varying amounts, the variations depending upon the conditions under which the muscle has been placed. Thus when muscle is removed from the body and the conditions are such that the removal of the products of ferment action cannot be effected, either by oxidation, owing to the predominantly anaerobic conditions existing, or by diffusion away from the seat of formation, then we should expect to obtain evidence of the accumulation of the products of degradation of the glycogen. The extent of the breakdown process will be determined by the activity of the ferments under the physical conditions existing, by the inhibiting effect on the enzymes of the products of their activity, and, in the case of acid production, by the reaction alterations in the medium. It is therefore evident that in intact, and still more in minced muscle tissue, living or dying under anaerobic conditions, the enzymatic products of the anaerobic degradation of glycogen should increase. The relative amounts of the glycogen and the products of enzymatic action on this carbohydrate in muscle which has been quickly removed from the body, and in which ferment action is checked by such a process as freezing, will give some information as regards the equilibrium established normally between the mother substance and the products of its enzymatic disintegration.

On examination of such muscle tissue it is evident that there are present, in addition to glycogen, substances which have been derived from it—namely, intermediate polysaccharides, hexoses, phosphoric acid esters of the hexoses, and lactic acid, not to speak of possible immediate

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precursors of the lactic acid. The work of Fletcher and Hopkins¹ may be regarded as the starting point of the modern investigations. These investigators emphasized, in the first place, the rapidity of the formation of lactic acid in muscle under anaerobic conditions, especially in minced muscle tissue; and, in the second place, the extent to which this process might be checked by rapid freezing. Their work also directed attention to the aerobic removal of lactic acid, and the significance which they attached to the so-called lactic acid maximum attracted the attention of other investigators, and has undoubtedly been of great value in the search for the immediate precursors of lactic acid. It is not necessary in this brief statement to refer at all fully to this work, nor to the investigations which rapidly followed, as they have been so well summarized in special articles and monographs by Embden,² Meyerhof,³ and A. V. Hill.⁴

The study of the rapidly changing phases of activity in stimulated muscle is an extremely difficult one. From the thermal standpoint the investigations of Hill and Meyerhof have given extremely valuable information. They have shown that the initial phase in a contraction is essentially an anaerobic one, and therefore it is during this stage that the products of ferment action on the glycogen may be expected to appear, and, up to the period of aerobic recovery, to accumulate. The periods dealt with in a single muscle contraction are so short that it is naturally impossible by chemical analytical methods to follow the process in the way that has been so successful in connexion with heat production. Although much ingenuity has been shown in the endeavour to trace these changes, there is still some difference of opinion as regards these initial anaerobic chemical changes during the contraction of muscle. The initial anaerobic heat production, according to Hill and Meyerhof, is associated with the formation of lactic acid from glycogen, and the neutralization of the former by the bases readily obtainable from the alkaline salts of such weak acids as the proteins and phosphoric acid. There is still some uncertainty as to whether the lactic acid production is the sole source of the initial anaerobic heat production.

Recently Embden and his fellow workers⁵ have dealt with this question, and have expressed the view that in muscle contraction the early exothermic changes in the anaerobic phase possibly have their origin in changes in the physical state of the intrafibrillar colloids. Whether such changes play a part in the initial anaerobic phase or not, it is necessary to gain as much information as possible regarding the cycle of changes through which the enzymatic degradation of glycogen takes place. It is for this reason that it appears to me advisable to refer more fully to recent work on the enzymatic processes in muscle carried out by Meyerhof and his school,⁶ as these investigations are gradually elucidating the problem which is so difficult of solution—namely, the role of the phosphates in the intermediate carbohydrate metabolism in muscle. To Embden and the Frankfurt school we are indebted for the knowledge that we possess regarding one (or more) of the phosphoric acid esters met with in muscle—the so-called lactacidogen. They have studied carefully the conditions under which this body is formed and undergoes disintegration, and have contributed valuable information regarding its general nature. For the first time the close association between alcoholic fermentation by yeast and the carbohydrate transformations in muscle was shown, and now we find that at each step in the further investigation of the role of the phosphates in the two processes, striking similarities in behaviour are becoming manifest.

It appears evident that an extremely important role is played by labile phosphoric acid esters in both mechanisms, but it is extremely difficult to determine from chemical analyses the exact nature of such bodies. The time has certainly not yet arrived for dogmatic statements in connexion with the relationship between the free phosphate and its labile and stable ester forms. Evidence, however, is accumulating that the chemical constitution of the stable form is different from that of the unstable one, and that the former may be regarded as the store of hexose phosphate which has passed out of one active stage in the production of lactic acid. The formation and disintegra-

tion of this stored more stable hexose phosphate may, however, be influenced by alterations in the condition of the living muscle tissue. The recent suggestion of Meyerhof and Lohmann (quoted by Neuberg and Leibowitz⁷) regarding the probable mechanism in the case of yeast fermentation is of interest, and a process of the same type may possibly occur in muscle. The suggestion is to the effect that in the first stage of the esterification process two molecules of hexose may react with two molecules of phosphoric acid to form two molecules of the monophosphoric acid ester, and that in the second stage one of the molecules of this ester may take up another molecule of phosphoric acid to form the diphosphoric acid ester, leaving one molecule of reactive sugar free. If such a process does occur, the diphosphoric acid ester may be regarded as the stable form, having passed out from the active cycle and become a storage product. The part played by such esterification processes in rapid changes of activity in muscle has still to be made clear, but from the study of the enzymatic transformations of the precursors of the esters, when the process is carried out slowly with the extracts of muscle prepared by the Meyerhof method, much valuable information has already been obtained. These extracts have been obtained from amphibian and also from mammalian skeletal muscle, and they can be tested under conditions when the main action is an amylolytic one, or one of esterification with or without lactic acid formation. I have also carried out a number of experiments with similar extracts from mammalian muscle, and in general my results confirm those obtained by Meyerhof, Lohmann, and other associated workers.

Some of the most striking results obtained from these investigations will now be referred to. The first change effected in the carbohydrate cycle is the amylolytic one, carried out by a ferment with a temperature range of activity greater than that of the others. Thus this action in mammalian muscle can take place at temperatures not only suitable for subsequent esterification (20° to 37°), but at higher temperatures (40° to 45°), and also at acid reactions which would inhibit the later processes of esterification and glycolysis. If the process be studied at 25° to 37° under conditions where there is a free supply of glycogen, and only the small amount of free phosphate extracted from the muscle by the cold saline solution, then following the amylolytic process there is an esterification one which is accompanied by lactic acid formation. If such an extract contained, for example, per cubic centimetre, slightly over 0.5 mg. H_3PO_4 in the form of free phosphate along with, say, 6 mg. glycogen, esterification would proceed slowly with an approximate equimolecular production of lactic acid and removal of free phosphate. This formation of lactic acid can proceed until practically all the free phosphate has disappeared. It is evident that in such a case a process is going on by means of which an ester in a stable form is being produced along with the lactic acid. Such a process might be accounted for by the production of a monophosphoric acid ester in the first place (the unstable form), followed by the taking up of an additional molecule of H_3PO_4 , so that in the process at each stage two molecules of the monophosphoric acid ester would be transformed into one of the diphosphoric acid ester, leaving a molecule of reactive sugar for lactic acid formation.

The stable hexose diphosphate so formed may, however, like the original ester in the muscle, be itself the source of lactic acid production, just as pure alkaline hexose diphosphate in solution may be broken down by muscle extracts to form in equimolecular proportions lactic acid and phosphoric acid. This process is essentially different from the first one as regards the necessary activating agents. For the first process the co-enzyme is required, and for the second it is not. The phosphoric acid set free in the disintegration of the hexose diphosphate may, however, be used up, on the addition of glycogen or starch, and thus the muscle extract may initiate again the combined processes of esterification and lactic acid.

What, then, is the effect of a fluoride addition to a mixture capable of carrying out such esterification and glycolysis? In those circumstances, just as in muscle tissue, esterification alone proceeds, not only without lactic acid

production, but very frequently with an actual disappearance of part of the acid originally present. The esterification process in this case has resulted in the formation of phosphate esters of a stable form.

A most interesting accompaniment of this purely esterification process, without lactic acid production, is an increase in acidity, and the swing in reaction is of the same order as in the case of the less complete esterification with accompanying lactic acid production which are the natural changes in the saline mixtures without fluoride. This rise in acidity in fluoride mixtures in which esterification is proceeding is undoubted. According to Meyerhof and Suranyi both the mono- and the di-phosphoric acid esters are stronger acids than orthophosphoric acid. Meyerhof and Suranyi compare this rise in acidity accompanying the linkage of phosphoric acid with the sugar with the well known increase in acidity which boric acid shows on condensation with mannitol. There can be no doubt that such a change does occur during the enzymatic process, and the acid swing on esterification, even in such artificially well buffered solutions as 0.025-0.030 molar phosphate, is a constant feature of fluoride esterification without any lactic acid production. The reverse effect of diminished acidity, produced by a simple hydrolysis of the stable ester without or with very little lactic acid formation, has also been noted by Meyerhof.

Before leaving this subject reference requires to be made to the action of such extracts on glucose, fructose, or other hexoses. Only under special conditions—and the same is true for muscle tissue itself—can the hexoses undergo esterification and glycolysis. The natural muscle extract, therefore, contains the necessary activators for the complete glycolysis of glycogen or starch, and not of the hexoses, or at least of those only to a slight extent.

Meyerhof has obtained distinct lactic acid production of the fermentable hexoses with fresh extract of rabbit's muscle. I have been unable to detect anything beyond a very slight acid production, and that not sufficient to change the reaction of a 0.025 molar phosphate solution. When, however, an activator obtained from yeast is added, these hexoses break down with great rapidity. In the process half is esterified and half broken down to lactic acid. The lactic acid production in the first phase is proportional to the amount of free phosphate present, and on the addition of more phosphate esterification increases.

It is therefore to be borne in mind that the normal carbohydrate present in muscle is the one from which the carbohydrate-phosphate transformations most readily start, and that, in the process of degradation of glycogen, esterification associated with a rise in acidity occurs, and also that labile esters are intimately concerned with lactic acid production. From what has already been said it is evident that the intermediate stages in glycolysis are concerned with labile ester forms which it may be impossible to identify in the chemical examination of resting or active muscle tissue.

In the study of the chemical changes accompanying activity of muscle investigators have naturally directed attention mainly to the glycogen, lactic acid, and the lactacidogen. Encroachment upon the glycogen store and equivalent production of lactic acid in anaerobic transformations has been established, and the fate of the lactic acid in oxidative recovery has been very thoroughly investigated by Meyerhof and Hill. The transformations of the intermediate body, lactacidogen, have been more difficult to elucidate. Being an intermediate body, the amount present at any time is conditioned by the balance struck between its formation and its breakdown. In any definite type of muscle, therefore, it is present at a fairly constant value, and even in activity the rate of its breakdown may only slightly exceed that of its formation.

Embden and his fellow workers have, in a series of investigations dealing with direct and indirect stimulation of isolated muscle preparations, studied the increments in free phosphate and lactic acid derived from the precursor lactacidogen. It is necessary to bear in mind that, as regards the phosphoric acid increments, these are set free by the breakdown of what is possibly the stable ester form. The preliminary investigations of the Eggletons² point to a possible unstable phosphate compound which they term

phosphagen, and which is apparently gradually broken down on stimulation, in rigor, etc. The inorganic phosphate values given by those who use the Embden technique, and any other method which involves a possible acid hydrolysis, according to these writers, include the phosphate bound in this labile form. Lohmann and Jendrassik, as well as Embden, have considered the possible hydrolysis of the hexose phosphates under those conditions, and this can at least be said—the more stable ester does not break down. The small number of analyses published giving the fluoride action on the free phosphates and phosphagen indicate that the low original free phosphate values obtained by these investigators remain unaltered, and phosphagen disappears—that is to say, a labile phosphatic compound has passed into a stable form. That the stable form is preserved in the Embden technique, and that additional phosphate and glycogen may be esterified to the stable form under fluoride, is undoubted. Certainly much more work requires to be done on the labile compounds before our knowledge of the initial changes in activity can be regarded as satisfactory.

According to the recent work of Embden the lactic acid rise in activity is not limited to the initial anaerobic period of activity. The accumulation of lactic acid which occurs in the separated muscle on stimulation is to a large extent prevented under conditions where the blood supply is not interfered with. As many of the earlier researches dealing with this subject are somewhat unsatisfactory, I have recently carried out a series of experiments dealing with the chemical changes in muscle, with blood supply intact, after stimulation and during the period of recovery. In all cases (in the cat) the muscle stimulated on one side could be compared with the same muscle on the resting side, or the stimulated one with the stimulated and subsequently recovered muscle on the other side. The stimulation was just sufficiently strong to bring out contractions, and the rate of the faradic stimulation was one or two per second. The periods of stimulation varied from fifteen minutes to two hours, with recovery periods of eight minutes' to two hours' duration. The results may very briefly be summarized. In all cases the water content of the stimulated muscle was higher than that of the resting one, and within eight minutes of the cessation of stimulation it showed a distinct decrease.

In practically every case, even after fifteen minutes' stimulation, the lactic acid content had risen and the glycogen fallen. In nearly every case the lactacidogen values after stimulation were below the normal. When the stimulated muscle was minced and subjected to the action of fluoride, the amount of stable hexose phosphate formed was smaller than in the case of the unstimulated muscle treated in the same way. This was most evident when excess of the precursors of the ester, glycogen, and phosphates was added to the mixture. Within an eight-minute period for recovery the muscle, which was practically free from glycogen when examined immediately after the stimulation, had commenced to replenish the exhausted store. The percentage of water fell during the recovery from 79.8 to 78.5 per cent., the lactic acid excess was being removed, but there was no early evidence of fresh building up of lactacidogen. After a longer period of recovery (twenty minutes) the storage of glycogen, the removal of excess lactic acid and water, and the return of the lactacidogen to its original value were all evident. The recovery of the esterification process under fluoride followed the restorage of glycogen by the muscle.

It appears, therefore, that during the period of stimulation there is an entrance of water which occurs rapidly, and this is accompanied by the changes which are characteristic of incomplete aerobic recovery. There can be no doubt that, after a period of activity which has resulted in practically complete removal of glycogen, the muscle is still able to contract almost as well as at the outset. The energy cycle of changes is evidently now starting with the products of the enzymatic disintegration of the glycogen.

It appears probable that changes in permeability in the muscle fibres are characteristic accompaniments of activity, and that even after moderate stimulation there is a disturbance in the water exchange resulting in retention of fluid. The free phosphate (determined by Embden's method) when calculated for water-free muscle shows a rise

during the period of stimulation and a fall during that of recovery. Throughout the periods of activity and recovery there must be a free interchange of anions between the muscle fibres and their environment, but the phosphate ion set free by disintegration of the hexose phosphate does not rapidly leave the muscle. During the period of recovery the excess free phosphate is used for esterification.

It is to be hoped that soon the nature of many of the chemical changes associated with activity which are still obscure may be cleared up—for example, the transformations in the sugars prior and subsequent to esterification, the nature of the immediate precursors of the lactic acid, and the mode of the endothermic conversion of lactic acid to glycogen.

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DISCUSSION.

Professor OTTO MEYERHOF (Berlin) considered that the significance of the chemical processes accompanying muscular activity, which were first laid bare by the pioneer work of Fletcher and Hopkins on lactic acid, lay chiefly in their supplying energy for the mechanical work. Summarizing a recent investigation in his laboratory, he said that energy was measured by heat of reaction, and therefore the problem arose of correlating the heat during and after contraction with the chemical processes occurring simultaneously. A. V. Hill had discovered that the heat was divided into two distinct phases of about the same magnitude, the first phase (so-called initial heat) coinciding with activity and independent of oxygen, and the second phase (so-called delayed heat, or heat of restitution) continuing for several minutes after the mechanical response, but only in the presence of oxygen. Professor Meyerhof had demonstrated some years ago that the first anaerobic phase was dependent on the formation of lactic acid from glycogen, the second phase on an oxidative process in which only a quarter of the lactic acid or a corresponding amount of carbohydrate was burnt, while three-quarters were resynthesized to glycogen. During the anaerobic phase there were liberated, on the average, 390 calories per 1 gram of lactic acid, which number was named the caloric quotient of lactic acid. When this acid was removed in the restitution phase, with combustion of 1/4 gram of glycogen hydrate, one expected $\frac{3,780}{4} - 390 = 555$ calories (3,780

representing the heat of combustion of glycogen hydrate per gram, and 390 calories the reversal of the heat liberated in the first phase). These 555 calories were 1.4 times the 390 calories of anaerobic heat. Thus anaerobic heat stood to oxidative heat in the proportion of 1 to 1.4; this proportion was similar to the findings of Hill and Hartree in their myothermic experiments. The speaker then considered the question as to how the 390 calories of anaerobic heat were to be explained. The difference of the combustion heats of dissolved glycogen and diluted lactic acid—the initial and final products of the reaction—amounted only to 180 to 185 calories according to the speaker's own measurements. Exactly the same value was found during the formation of lactic acid in cut muscle, suspended in phosphate solution; and also in recent experiments, in which the glycogen was fermented by the muscle enzyme in aqueous solution. Undoubtedly the mere transformation of glycogen into lactic acid only accounted for about 180 calories. But in the intact muscle the lactic acid reacted with muscle protein according to the abbreviated equation:

by de-ionizing the protein. If the whole of the lactic acid reacted in this way 140 calories would be liberated, corresponding to the heat of de-ionization of proteins. But, as was found in collaboration with Dr. Lohmann, only half of

the lactic acid formed during fatigue was neutralized by alkali proteins, the remainder by phosphate and other buffers. Therefore only about $70 + 10 = 80$ calories were to be expected from neutralization. Altogether 260 to 270 calories were covered by known reactions, and for the origin of about 120 calories the explanation was lacking. Attempts for many years to find a higher heat of de-ionization in the living muscle or a measurable amount of energy by colloidal changes had been in vain.

P. and G. P. Eggleton in the Institute of Professor A. V. Hill, and Fiske at the Harvard Medical School, had simultaneously found that two-thirds to three-quarters of the whole phosphate in muscle which was believed to be inorganic was in reality in a very labile combination, which, as Fiske had demonstrated, contained besides phosphate also creatine in equivalent amount. This labile compound, named by the Eggletons "Phosphagen," was decomposed in large part during the anaerobic fatigue; during the oxidative restitution it was rebuilt similarly to the carbohydrate. In experiments which were made in collaboration with Dr. Lohmann, concerning the breakdown of phosphagen by muscle enzyme, Professor Meyerhof had found that sugar and lactic acid were never formed in this way. Preparations of phosphagen, about 90 per cent. pure, showed a molecular weight, dissociation curves before and after splitting, and kinetics of hydrolysis which agreed with the simple formula of 1 molecule of phosphate and 1 molecule of creatine, obviously bound together by the amino group of the creatine; thus it was a phosphamide with the structure $R.NH-PO(OH)_2$.

In confirmation of the suggested constitution was the fact that all the known simple phosphamides behaved similarly; they were stable in alkaline and unstable in weakly acid solutions. The splitting of phosphagen into phosphate and creatine gave a heat formation of 150 to 160 calories per 1 gram of phosphoric acid; on the other hand it was found, in confirmation of the work of the Eggletons, that during muscle activity the ratio of phosphagen breakdown to lactic acid formation was not constant, but decreased with fatigue. However, in an anaerobic fatigue of average degree leading to an accumulation of 2 mg. of lactic acid in 1 gram of muscle, 80 to 90 per cent. of the available phosphagen was split. This meant a production of 1.5 mg. of inorganic phosphoric acid, or 0.75 mg. of phosphagen phosphoric acid per milligram of lactic acid, which gave 120 calories. This was exactly the value which was so far unaccounted for as a portion of the "caloric quotient." Thus the heat of contraction was caused not only by the anaerobic splitting of carbohydrate and associated physico-chemical reactions, but also by a second metabolic process, till now completely unsuspected—namely, the formation of creatine from a precursor. It followed, on the other hand, that the caloric quotient could not be exactly the same during the whole course of fatigue, but must sink from a higher to a lower value corresponding to the diminishing amount of phosphagen split. The ratio between phosphagen split and lactic acid formed was about twice as high in the beginning of fatigue as in the calculation used above. The decrease of the caloric quotient in higher degrees of fatigue was found in the speaker's earlier experiments; an increase on very short stimulation was indicated, but could not be proved because of the insufficient accuracy of the measurements; he stated that it is purposed to reinvestigate this shortly. All voluntary muscles formed lactic acid from glycogen during mechanical work, while the occurrence of phosphagen was limited. Eggleton had not found it in the muscles of invertebrates, in which E. Mellanby had shown that creatine was lacking. The speaker had found that the muscle of the crab (*Astacus*) contained no phosphagen, but another phosphate compound which behaved similarly in chemical and physiological respects and was apparently a substitute for phosphagen. Probably, therefore, phosphagen-like bodies played a universal part in the activity of striated muscle. It was most remarkable that, while the main part of phosphagen was restored only in oxidative recovery, a small part of the amount split during the tetanus was immediately afterwards rebuilt, apparently in the moment of relaxation. The energy for this might be afforded by lactic acid formation, or the restabilization might be immediately due to

the mechanical and elastic change corresponding to Hill's heat of relaxation. Although the older hypothesis of a double mechanism in muscle, tonic and contractile, due to creatine and lactic acid respectively, had not been verified in these experiments, some dualistic theory regarding the part played by creatine and lactic acid formation in contraction apparently had now become necessary. There were doubtless several other metabolic changes during activity of muscle; such was the formation of ammonia studied by Tashiro, Embden, and Parnas. Professor Parnas in Lwow (Poland) had found that during injury, rigor and also during mechanical work ammonia was formed, in quantities of about 1 molecule NH_3 to 14 molecules of lactic acid, in proportion to the amount of work done. But the amount of ammonia was quite independent of the presence or absence of oxygen, and remained unchanged during recovery. This NH_3 was given up to the blood stream in the intact animal and was apparently the cause of the increased nitrogen metabolism during work, found by Rubner, Cathcart, and others. While this reaction as well as others completed the intimate picture of the metabolism of working muscle, he believed that the chemical happenings decisive for the supply of energy were now quantitatively known. In addition to the breakdown of glycogen and its resynthesis in recovery, the splitting of phosphagen and its rebuilding from creatine and phosphate furnished an important part of the energy supply of muscle; both together were responsible for the heat of contraction.

Professor G. EMBDEN (Frankfort-on-Main) directed attention to the problem of ammonia production in muscular contraction. The question arose during work on lactacidogen, the muscular substance which formed lactic and phosphoric acid. The extraction of this substance from fresh muscle was very difficult because it was associated with a nitrogen-containing body; finally, however, the two substances were completely separated. The lactacidogen could be isolated as a crystalline brucine salt and as an amorphous barium salt, of a hexosemonophosphoric acid of a special kind. The nitrogen-containing substance was definitely identified with an already known body—namely, adenosinphosphoric acid, which had not till now been found as a mononucleotide in nature. Adenosinphosphoric acid seemed to occur in a rather large amount in fresh muscle, though during its isolation the greater part was lost. The fact that adenosinphosphoric acid could be got especially out of quite fresh muscles, while inosinic acid was obtained from the extraction of muscles not quite so fresh, led to the conclusion that there was a very close biological connexion between the two substances, which, as the formula showed, only differed in this respect—that in the purine nucleus in place 6 the inosinic acid had an hydroxyl group and the adenosinphosphoric acid an amino group. The adenosinphosphoric acid could easily pass into inosinic acid by simple hydrolytic de-aminization, and this led to the idea that the formation of ammonia in dying muscles, previously observed and recently confirmed by Gad Andersen, might have its origin in this de-aminization. Gad Andersen had thought that this *post-mortem* ammonia formation might have its origin in urea, while Meyerhof, who had found ammonia formation in isolated diaphragm muscle, believed that it came from proteins. Riebeling, Selters, and Embden had shown that the spontaneous formation of ammonia in dying muscle was greatly increased by the addition of the sodium salt of adenosinphosphoric acid. Gerhard Schmidt had been able to transform adenosinphosphoric acid into inosinic acid by the effect of a ferment solution procured from muscle. These processes, which were originally found in dying muscle, were later recognized as characteristic accompaniments of activity. The lactic acid formation in dying muscle had long been known, when Fletcher and Hopkins investigated the formation of this acid during activity. Also the production of inorganic phosphoric acid was at first recognized as a dying phenomenon and only later as a characteristic accompaniment of every muscular contraction. The close relationship between chemical processes in active and in dying muscle had led the speaker to investigate whether there was ammonia formation in active as well as in dying muscle. Experiments by Riebeling, Embden, and Wasser-

meyer had shown that severe fatigue of isolated frog muscles was associated with a very great increase in the ammonia content. Quite independently Parnas and Mozolowski had described ammonia formation in the fatigue of isolated frog muscles, and it could also be demonstrated during muscular activity in the living frog. In the gastrocnemii of frogs which did not jump much the ammonia content was about 2.2 mg. for 100 grams of muscle. In frogs killed forty-five minutes later it was increased to 5.1 mg., and seventy-five minutes later the ammonia reached 9 mg. The resting of previously fatigued muscles was followed by the disappearance of ammonia, both in isolated muscles and in living animals; the ammonia content in one case was 13.8 mg. before, and after one hour's rest 9.6 mg. These frogs had been examined in May; in the other summer months ammonia never increased so strongly, owing to the frogs being less lively. Thus in June the ammonia content was 2.6 mg. before, and 2.1 mg. after rest. Great variations were only evident in the month of May, at which time the frogs were very much more lively than at any other time. At every season, however, the quantity of ammonia was greater in lively frogs than in quiet ones; and in the *esculenta* species more than in the *temporaria*. In general, less was found during the night than in the day, and a well marked concentration in living frogs might be regarded as a sign of fatigue.

When the gastrocnemii of both sides were tetanized for a short time in the same circuit, and the muscles of the one side then immersed in liquid air at the height of the tetanus, while the muscles of the other side were fixed, after a resting period of ten to sixty seconds the ammonia content of the muscles which were immersed later was found to be much lower than the others. This result was obtained in five winter experiments performed in frogs which were in good condition. Recent experiments by Miss Karstensen and Miss Schumacher indicated that the ammonia split off by a quite short tetanus was not rebuilt, or at least not completely rebuilt during relaxation. In these experiments the first muscle was not immersed at the height of the tetanus, but immediately after relaxation, the second one minute later. In all experiments in which the muscles relaxed immediately after the cessation of the stimulation less ammonia was found in the muscles later immersed. It seemed as if the muscles of frogs kept for a long time in the laboratory were less able to resynthesize the ammonia split off during tetanus, and the same was true for frogs caught only a few days before the experiment during summer heat. Such muscles behaved after one short tetanus like fatigued muscles. Therefore it seemed necessary to perform experiments concerning the reversibility of the ammonia formation during muscular contraction only on such frogs which had been caught immediately before the experiment.

From the experiments mentioned it was evident that during muscular contraction not only lactic acid and phosphoric acid were formed, but also ammonia appeared. Twenty years previously Slosse, working on dogs, had also found an augmentation of ammonia during muscular activity, and recently Tashiro had shown that during stimulation by single induction shocks isolated frog muscles gave off more ammonia than resting ones. The latter experiment could be explained, apparently, as well by augmentation of ammonia in the moment of contraction as by a diminution of muscular acidity at the same moment. Some years previously it was found that the katabolism and anabolism of hexosephosphoric acid were ruled by ions. Lehnartz had been able to show that adenosinphosphoric acid brought about much more rapidly than any other known substance disappearance of inorganic phosphoric acid. These experiments were performed on the press juice of rabbit muscles. It seemed probable that this ionic effect of adenosinphosphoric acid might be of the greatest importance for the rebuilding of lactacidogen during muscular work. In the experiments of Lehnartz the phosphoric acid was determined in strongly acid reaction. The differences, therefore, in the phosphagen content, which, as was known from the work of the Eggletons, was rapidly split in strongly acid reaction, could not be determined. The experiments should accordingly be repeated with special attention to the phosphagen change. Nothing definite was

known about the energy change effected by the ammonia formation in muscular contraction. The hydrolytic deamination of adenosinphosphoric acid in the formation of inosinic acid, an endothermic reaction, could be toned down by secondary processes following the de-amination. As regards the importance of ammonia formation in the energetic changes, experimental investigation was required to determine whether all the ammonia formed in muscular contraction came from adenosinphosphoric acid, or whether there were other sources of ammonia. Unpublished experiments by Wassermeyer emphasized that there was no other ammonia-forming substance than adenosinphosphoric acid (or perhaps adenosin). In every future attempt to explain the entire process of muscular contraction from a chemical standpoint attention would have to be paid to the ammonia formation during contraction.

Sir F. GOWLAND HOPKINS (Cambridge) remarked that there was a time-honoured assertion that the biochemist could not hope to deal with the actual events in living tissue, because from the very moment his methods were applied to them the tissues ceased to be alive. This assertion had been shown to be baseless by the advances already made in the chemistry of muscular activity. Progress had been so real that they had, perhaps, become unduly light-hearted in contemplating the problems; recent discoveries had shown that there were complexities hitherto unsuspected. On some important points sharp differences of opinion were developing, but since those who disagreed were experimentalists and not theorists, ultimate agreement would surely be reached. The speaker referred to the study in his laboratory of muscles which, after a prolonged stay in oxygen at low temperatures, had become completely insensitive, their irritability being again restored by immersion in solutions of certain electrolytes. The facts observed seemed likely to throw light upon the conditions which determined a normal response to a stimulus.

Professor T. H. MILROY, in reply, referred briefly to the nature of the linkage of the phosphoric acid in the compound described by Professor Embden, and commented on the importance of the recent investigations which had just been reported. Within a comparatively short period our knowledge of the chemical changes in muscular activity had been greatly extended.

MISCELLANEOUS PAPERS.

FOLLOWING the discussion on the chemical changes accompanying muscular activity a number of short papers dealing with physiological and biochemical subjects were read. Brief abstracts of some of these are printed below.

THE CONSTITUTION OF THYROXINE.

Dr. C. R. HARINGTON (London) detailed briefly the steps which led up to the isolation of thyroxine in the pure condition. It appeared that the first indication that the physiological action of the thyroid gland was concerned in any way with iodine was obtained by Kocher (1895), who made the observation that the administration of iodine had a favourable therapeutic effect in cases in which the thyroid function was deficient. In the same year the significance of this observation was extended by the work of Baumann, who demonstrated the actual presence of iodine in the thyroid gland, and was further able to indicate a rough parallelism between the iodine content of various preparations of the gland and their physiological activity. This discovery made it at once apparent that any attempt to isolate the active principle of the gland involved a systematic pursuit of the iodine. Baumann himself started experiments in this direction, and found that simple extraction of the gland with water and alcohol removed relatively little of the iodine, which, therefore, was apparently bound up more or less firmly with the proteins. On the other hand, hydrolysis of the gland with dilute sulphuric acid yielded a product (iodothyronin) which contained variable but larger amounts of iodine (5 to 14 per cent.) than the original gland, and also showed an enhanced physiological activity. In the light of present knowledge this substance was to be regarded as impure thyroxine.

A similar substance was obtained by Hutchinson (1898) by peptic digestion of the gland, and by Oswald (1902) by acid hydrolysis of an iodine-containing globulin which he extracted from the gland with dilute saline. By no method, however, could iodothyronin be prepared with a constant chemical composition. No further progress was made with the problem until, in 1919, Kendall announced the isolation of a pure crystalline substance from the thyroid which contained 65 per cent. of iodine, and which exhibited in a high degree the typical physiological action of the gland. On the basis of elementary analysis Kendall ascribed to this compound the empirical formula $C_{15}H_{10}O_4NI_4$; he further propounded a constitutional formula:

regarding it as a derivative of oxindolepropionic acid (hence the name "thyroxine"), and as being ultimately derived from tryptophan. This formula, however, presenting as it did inherent chemical improbabilities, was advanced without any experimental support.

The continued absence of any evidence as to the true chemical nature of thyroxine led Dr. Harington, in 1925, to take up the problem of its constitution. For this investigation the primary requirement was the possession of a fairly large amount of the pure substance, and a method had therefore to be devised which would give a better yield than the very small one obtained by Kendall. The method of the latter worker consisted in hydrolysis of the gland with 5 per cent. sodium hydroxide followed by a complicated process of salting out of the thyroxine, first as the barium salt and then as the sodium salt, the ultimate yield being 0.001 per cent. of the original gland. It was found that a considerable improvement was effected by substituting barium hydroxide as the hydrolytic agent and by conducting the hydrolysis in two steps, a preliminary mild hydrolysis of the whole gland being followed by an intensive hydrolysis of the partially purified product. In this way about twenty-five times Kendall's yield of pure thyroxine was obtained, and it became possible to accumulate a sufficient quantity of material for the investigation of its chemical structure.

The first step in this investigation was the removal of the iodine; this was accomplished by means of hydrogen and palladium, a method which could easily be shown to induce no secondary changes in the molecule, and which therefore yielded a product which was certainly identical with thyroxine, save for the substitution of the iodine of the latter by hydrogen. This iodine-free product (desiodothyroxine) proved to have the empirical formula $C_{15}H_{15}O_4N$, which, in turn, indicated that the formula of thyroxine must be $C_{15}H_{11}O_4NI_4$. Desiodothyroxine further turned out to be an α -amino-acid with one phenolic group and two benzene rings in the molecule; a systematic process of degradation indicated, indeed, that the formula was

that is to say, that the compound was the *p*-hydroxyphenyl ether of tyrosine. The correctness of this hypothesis was proved without great difficulty by the synthesis of this compound and the identification of the synthetic product with that obtained from thyroxine. Thyroxine was therefore proved to be a tetra-iodo derivative of the above compound.

The synthesis of desiodothyroxine did not, however, assist in the synthesis of thyroxine itself, since the four iodine atoms could not be introduced directly, nor could direct evidence be obtained as to the positions occupied by these atoms. The fact that two iodine atoms were apparently taken up directly with ease, together with various other considerations, led to the hypothesis that, in thyroxine, the iodine atoms were present in pairs, one in each of the benzene rings A and B. Since it was evidently the inner ring B which was resistant to direct iodination,

the problem of the synthesis of thyroxine resolved itself into the problem of the repetition of the synthesis of desiodothyroxine with the two iodine atoms already in position in ring B. The first compound of the desired series was obtained by combining the monomethyl ether of hydroquinone (I) with tri-iodonitrobenzene (II):

a reaction which was rendered possible by the preferential mobilization of the middle one of the three iodine atoms in (II) by the presence of the nitro group. The resulting nitro-compound was converted, by standard reactions, successively into the corresponding base, nitrile, and aldehyde, from which, by a modification of Erlenmeyer's amino-acid synthesis, there was prepared the compound

According to our hypothesis, this compound required only the introduction of two more iodine atoms in order to convert it into thyroxine. On direct iodination in ammoniacal solution it took up, indeed, two atoms of iodine, which could only have entered the positions adjacent to the phenolic group in the outer ring, giving therefore

The resulting compound was chemically and physically indistinguishable from thyroxine. The final identification was accomplished by clinical tests carried out by Professor Murray Lyon, the result of which indicated the complete similarity of the synthetic product with that isolated from the gland.

Two points arose in connexion with the proof of the constitution of thyroxine. The compound was an amino-acid, and, in the thyroid gland, it was almost undoubtedly present in combination in a peptide or protein, which was in accordance with the views of the earlier workers on the subject. Secondly, by virtue of its structure as an α -amino-acid it was capable of existing in optically active modifications. The compound isolated from the gland, owing no doubt to the alkaline hydrolysis which was employed, was racemic, as was also the synthetic compound. Dr. Harington added that work was at present in progress on the resolution of thyroxine into its optically active components, and it would be interesting to see whether one of these might exhibit a higher degree of physiological activity.

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PHYSIOLOGICAL CONSIDERATIONS IN HIGH BLOOD PRESSURE.

Professor R. J. S. McDOWALL (London), in a communication on physiological considerations in high blood pressure, stated that the chief evidence that the problem was primarily a physiological one was that in these cases of high blood pressure there might be intervals during which the blood pressure was normal, and that treatment of often brief duration might cause the pressure to fall.

The late Professor Starling had dealt with the problem from the physiological standpoint and had indicated how the high blood pressure might be accounted for as an over-action of the vasomotor centre. This view had recently

been supported by Professor McWilliam, who had at the same time given one of the best reviews of the subject in existence.

Professor McDowall said that it would be interesting to determine how the vasomotor centre was stimulated to excessive activity. Starling had suggested that minute clots in the medulla would explain this overaction, but this could not explain the intermissions, or the effects of treatments, and the fact that no other function of the medulla was affected. Clinicians recognize two great factors in the causation of hyperpiesis—namely, toxæmia and mental stress—the former cause having been championed in this country of recent years by Dr. Batty Shaw and the latter by Lord Dawson.

Professor McDowall dealt first with toxæmia and the possibility of producing high blood pressure in animals by the injection of substances likely to occur in the body. While it was not necessary to consider the artificial injection of adrenaline, the effect of which was evanescent, various workers had attempted to find evidence of the existence of a pressure substance in the blood of cases of hyperpiesis, but on the whole the evidence was negative. He said that the substance which would produce a lasting high blood pressure in cats was histamine, which, as shown by Dale and Richards, dilated capillaries. If, however, an animal was anaesthetized with chloralose, and time given for all the effects of the sensory stimulation of the operation to pass off, a temporary fall of blood pressure was obtained, succeeded by a prolonged rise. This rise was believed to be due to an over-compensation of the vasomotor centre. The speaker had obtained definite evidence that when the blood pressure had returned to or above normal the aorta had constricted, as indicated by an increased velocity of the pulse wave, and that there had been a constriction of the vessels of the skin. There was brought into operation exactly the same mechanism as was utilized in haemorrhage—a constriction of the arteries, which maintained the arterial pressure, and reduced the venous pressure. From the work of Kellaway and Cowell and the subsequent work of Dale and Burn there seemed little doubt that the activity of the vasomotor centre was reinforced by the action of adrenaline secreted by the animal itself. Such over-compensation did actually occur in haemorrhage. If 5 to 10 c.cm. of blood was removed from a cat the blood pressure, taken several hours later, was not infrequently found to be over 200 mm. of mercury. A similar observation had been made by Dr. Anrep on dogs. Several early workers on the effects of posture, including Professor Leonard Hill, had described instances of over-compensation and a raised blood pressure on the assumption of the erect posture.

In considering the mental factors Professor McDowall remarked on the familiar effects of emotion on the circulation, the cardiac acceleration, and the pallor of fear; this latter was often very clearly seen in children. It did not, however, appear to be generally appreciated that mental conditions which gave no appreciable sensations might cause constriction of vessels. This was first shown by Mosso, and it was interesting to note that the diminution of the volume of the limb due to a minor emotion was the first experiment ever made by Mosso on the plethysmograph.

During the last few years several workers in Professor McDowall's laboratory, Densham and Wells especially, had established the fact that what used to be known as the psycho-galvanic reflex was really a similar phenomenon caused by constriction of the vessels of the skin. For example, a pinprick, actual or only threatened, caused an enormous fall of the electrical resistance of the skin; in fact, any form of mental stress or effort brought about a similar result. Mosso, indeed, in order to convince a sceptical friend, had demonstrated that this vaso-constriction occurred in passing from the translation of "seen" to "unseen" (Greek). The high blood pressure of mental stress might be brought about by a similar mechanism. Lord Dawson had found that in certain schoolboys there was a considerable rise in the blood pressure above normal during examinations.

While the exact nature of the whole phenomenon was still uncertain, yet, from the relation of the threatened to

the actual pinprick, Professor McDowall suggested that the emotions which caused this vaso-constriction might be looked upon as conditioned sensory stimulations. In physiology it had long been known that actual sensory stimulation caused a rise of blood pressure. It was very interesting that the rise of blood pressure which could occur under conditions of mental stress might be considerable. For months he had his blood pressure taken daily, and quite accidentally it was found that on one occasion before an important lecture his blood pressure rose from a normal of 110 to 160, and remained up for several hours. Previously Leonard Hill, and more recently Gillespie, had shown similar rises of blood pressure in response to mental effort. He had little doubt that this rise of blood pressure was designed for the facilitation of muscular activity, which in a civilized life did not necessarily accompany or succeed mental stress.

Their next step had been to determine how far these two causes might influence ordinary individuals at work. The investigation was just in its infancy, but even already some very suggestive points had cropped up. His colleague Wells had found that in some individuals there was a diurnal variation, which they believed to be associated with mental stress. There was often in women a pre-menstrual fall and a post-menstrual rise, and, what was extremely interesting from the toxæmic point of view, a definite influenzal fall and a post-influenzal rise. The same individuals when fatigued did not show the diurnal variation.

These observations were being extended to other forms of toxæmia with a view to determining if the response to other toxins was the same, and, if so, to what extent different individuals responded similarly.

NATURAL ARREST OF HAEMORRHAGE.

Professor JOHN TAIT (Montreal), in a communication dealing with the natural arrest of haemorrhage from a wound, said that throughout the animal series there were arrangements whereby any accidental wound of the blood-containing system became plugged by the intervention of the blood. The common belief was that the plasma was particularly and exclusively involved in closing any accidental orifice. In all the invertebrates possessed of blood or body fluid it was the corpuscles that played a part; they adhered to the edge of the wound in the vessel, and by successive accumulation became aggregated into a resistant gummy mass, which acted as a plug. A similar phenomenon also occurred in the case of vertebrates, the corpuscles involved being the special elements called spindle cells or thrombocytes. The question, then, arose whether coagulation of the blood plasma assisted in arrest of haemorrhage. Where the bleeding occurred into the meshes of areolar or connective tissue coagulation was induced. If the vessel previous to puncture had been carefully denuded of its adventitial sheath the only method of arrest was by agglutination of thrombocytes—platelets in the case of the mammal. The speaker illustrated his remarks with lantern slides.

THE CIRCULATION RATE.

Dr. H. WHITRIDGE DAVIES (Leeds) and Professor B. A. McSWINEY (Leeds) contributed a joint communication and described experiments in which estimations of the circulation rate in dogs were made by the Henderson-Haggard ethyl iodide method. The results showed very considerable disagreement with those determined simultaneously by another and more reliable procedure. It was found that the most important fundamental assumptions of the ethyl iodide method were erroneous; thus the coefficient of distribution of ethyl iodide between alveolar air and arterial blood was found to be approximately 5.2, instead of 2.0 as stated by Henderson and Haggard. Moreover, considerable quantities of ethyl iodide were found in the mixed venous blood. Under certain conditions the difference between arterial and mixed venous concentrations of ethyl iodide was approximately equal to the alveolar concentration multiplied by two. This fact would account for the reasonable results obtained in many instances, the two errors tending to cancel one another. Such a cancelling was, however, purely fortuitous and could not be relied upon. In some cases, where pulmonary embolism occurred, the relation between the concentration of ethyl iodide in the arterial

blood and in the mixed alveolar air was markedly disturbed. Similar disturbances would occur in any pathological condition in which the normal relationship between alveolar ventilation and pulmonary circulation was upset. The automatic method of sampling alveolar air described by Henderson and Haggard, when applied to dogs, gave results which were remarkably consistent and reasonable. The alveolar carbon dioxide pressures agreed closely with those of the arterial blood obtained indirectly by determinations of its carbon dioxide contents and dissociation curves.

OPTIC NEURITIS.

I.—ETIOLOGY: DIAGNOSIS: PROGNOSIS.

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By the term "optic neuritis" the oculist usually means a certain type of morbid changes which he sees at the optic disc on examination of the fundus of the eye. He recognizes, however, that parts of the nerve other than its distal end, though not visible with the ophthalmoscope, are also liable to be affected by changes such as oedema or inflammation, and in speaking of these cases he usually employs the term "retrobulbar neuritis."

The optic disc has been perhaps the most carefully studied of all the parts of the fundus oculi, and naturally very complete descriptions of the morbid appearances have been given, and even the relation of these appearances to local pathological and anatomical findings have been fairly well made out, though opportunities for the anatomical and pathological examination of early cases of optic neuritis are of very rare occurrence.

During the long time that has elapsed since the early descriptions of morbid appearances at the disc a great deal of confusion seems to have gradually developed, owing to a vague, uncertain, and variable nomenclature. New names intended to define or describe certain types of disc change have been introduced, and terms such as "optic neuritis," "papilloedema," "choked disc," "papillitis," and "neuro-retinitis" are now freely used. The sense in which the oculist uses these terms will depend a great deal on the view he has formed, or has been taught, regarding the etiology or the pathological significance of the changes he has under observation. In my opinion the classification of cases of optic neuritis should be based on a full investigation of the cases as a whole, and not merely on the observer's idea of the type of disc changes present. When the cases are studied from this wider point of view it will be readily admitted that those associated with increased intracranial pressure may be at once placed in a class by themselves. This differentiation depends not only on the type of the disc changes—for example, the amount of swelling—but also on the examination of the vision (the absence of any pronounced visual disturbance in the early stages being of paramount importance in the diagnosis). Many of the older case records where optic neuritis or double optic neuritis is noted as occurring, but without proper record of the presence or absence of visual symptoms, leave the reader guessing as to the significance to be attached to the term "optic neuritis."

With regard to the study of the changes at the disc I can well believe that the use of the Gullstrand ophthalmoscope is of the very greatest importance, and I hope that the younger school of ophthalmologists in this country will have more opportunity of using this valuable instrument than their predecessors have had. While freely admitting that many cases of disc change can be instantly and correctly interpreted as due to intracranial pressure, there are many cases where, especially in the early stages, the diagnosis cannot be made with any certainty from the disc appearances. Vision, at least in the early stages, is in the vast majority of the cases little if at all affected.

* The opening paper of a discussion on optic neuritis in the Section of Ophthalmology at the Annual Meeting of the British Medical Association at Edinburgh. The president, Dr. A. H. H. Sinclair, was in the chair.