on the day after etherization; (2) and a considerable rise on the two subsequent days.

So much is this the case that according to this table, on the day after the operation the total nitrogen excretion is little more than half the excretion on the day before the operation, whereas on the fourth day the total nitrogen excretion is practically double the normal. In only four cases was the rule of a fall on the day after the operation not observed. With reference to the subsequent rise, although Table IV. shows that the maximum occurred on the fourth day, this was not absolutely true in the individual cases, for in six cases the maximum occurred on day 3. It may therefore be concluded that a rise in total nitrogen excretion may be expected on days 3 or 4.

EXCRETION OF UREA.

In spite of the dogmatic assertions that have been made as to the behaviour of urea excretion after anaesthesia, it has been impossible in this set of experiments to speak with absolute certainty.

The total urea columns in Tables III and IV show that there is a general tendency for urea to fall on the day after etherization, and in Table III this fall occurs in 9 out of 13 cases. In half of the cases which show a rise, that rise is only fractional. As might be expected from the total nitrogen results, in every case except ix and xiii the maximum urea excretion was reached on days 5 and 4, and was in excess of that on day 1. The percentage columns in Table IV, to which special attention is drawn, show that there is a general tendency for the percentage excretion of urea nitrogen on day 2 to rise above, and on day 4 to sink far below, its percentage on day 1. Such a fall, in the face of the average doubled output of total nitrogen on day 4 and the low amount and low percentage excretions of uric acid nitrogen, is most significant, and points to a profound change in the composition of the urine, in virtue of which nitrogen tends more and more to be eliminated by other bodies than urea. In the individual cases, such a fall in percentage on day 4 is shown in 8 cases out of 13.

EXCRETION OF URIC ACID.

One of the most interesting results in the whole investigation has been that in connexion with uric acid. In every single case the anaesthesia has been followed by a marked rise in the percentage excretion of uric acid, and in every case but one (xii) the maximum is reached on the day after the operation. Naturally, this result is very well marked in the composite case, which also shows clearly that the average daily excretion on days 2, 3, and 4 is almost always in excess of that on day 1. The regularity of this increase in percentage excretion of uric acid contrasts so strongly with the irregularity observed in the individual cases in respect of the excretion of urea and xanthins as to suggest the existence of some constant physiological factor in the case. Halliburton includes amongst conditions leading to an increase of uric acid (a) diminution of oxidation processes, (b) processes leading to metabolism of nucleins. The former condition certainly obtains in ether administration by the closed method; the latter is the necessary consequence of most surgical operations and of the starvation diet accompanying them. Besides which in two cases (not included in my series) prepared for operation, but not operated on, a distinct percentage rise of uric acid nitrogen took place on day 2 and day 3 respectively. This suggests that the nervous state of the patient may have something to do with the phenomenon.

EXCRETION OF XANTHIN BODIES.

From the method in which these bodies were calculated it will be seen that in total amount and percentage they must vary inversely as the urea, and that in consequence their accuracy is at best relative, and stands or falls by the correctness of the urea estimations. It therefore merely remains to attempt to account for their presence and proportionate amount.

Mr. Tyrrell⁵ quotes a patient's statement with approval, that "taking ether for an hour and a-half is very hard work," and there certainly is an analogy between the effects of prolonged etherization and exhausting bodily work.

Drs. Dunlop, Paton, Stockman, and McAdam state that in all persons severe muscular exercise is followed by increased output of total nitrogen and of urea, but that if the person is out of condition the output of uric acid and extractives is also increased.

Whilst probably none of the cases in the present series were in any athletic conditions, it is noteworthy that of the

whole series those five cases whose total xanthin percentages for the four days exceed the average as determined by the composite table include both the tuberculous cases and the necrosis and sarcoma cases (Cases i, vi, ix, and xi), and only one case who was presumably in fair condition, namely, Case x. The other cases were in general health or as (in Case v, bilharzia) had been for a long time under hospital treatment, which is clinically known to put a patient in the very best position for standing an operation or anaesthetic.

I have only in conclusion to tender my sincerest thanks to Dr. W. S. Lazarus-Barlow for permitting me to make all the estimations in the Westminster Hospital Clinical Laboratory, and for much help and advice; and to the staff of the hospital—most especially to Mr. Spencer—for permission to make use of the cases under their care.

I also desire to state that I have previously worked at urea excretion in collaboration with Dr. Eldon Pratt, now of Henfield, Sussex. My departure on active service brought our joint experiments to an abrupt conclusion. I have therefore left the question of publication entirely in his hands.

REMARKS.

1. Percentage of total nitrogen contributed by urea. "Eighty-six per cent. is not below the average determined by Gumlich and Bohland."⁷

2. Average daily excretion of uric acid as here determined may be compared with Smith-Jerome's determinations. In my cases the diet is certainly not highly nitrogenous, and the uric acid average compares fairly with that given by him both for "ordinary" and "nuclein" diets.⁸

3. If it be granted that my results coincide fairly with those of the above-mentioned authorities as to urea and uric acid, my reduced figures with regard to xanthin bodies may be allowed as fairly accurate. They are, I think, larger than is usually admitted.

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THE PROCESS OF CHEMICAL SYNTHESIS IN LIVING THINGS.*

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SOME years ago—it was in 1896 that I began experimental work on this subject—I was struck by the fact that nothing was known of the manner in which the synthetic process occurred in living organisms, although, concerned as it must be in such elementary functions as tissue nutrition and the growth and multiplication of the tissue units, it is ultimately the most fundamental phenomenon of life. Building up and breaking down of tissue considered together constitute what is known as metabolism, and are the constant characteristics of all forms of life, down to the simplest organism known. They must, too, be considered together, for as it is the object of this paper to set forth, they are but phases of one and the same process, and it is because the process of breaking down has not been fully understood in the past that the process of building up has not been seriously studied at all, but, on the contrary, has been relegated to a realm outside the exact sciences, and ascribed to a mysterious "vital" force of an only less mysterious protoplasm.

Foster, in his introduction to his *Textbook of Physiology* (ed. v, 1891), divides physiology into two great divisions, one having to do with the renewal of substance and the replenishment of energy, the other having to do with the setting free of energy. With regard to the general problem of how metabolism of living substance takes place, he says, "the answers which we can at present give can hardly be called answers at all."

From theoretical considerations alone, I was able to construct a hypothesis for the anabolic process in which intracellular ferments played a leading part, but it required for its justification the experimental proof that ferment action, at that time known only in connexion with chemical change in

* Abridged from a Thesis for the M.D. degree in the University of Cambridge.

a single direction, was, in fact, a reversible process, and that synthetic changes of metabolism, just as the analytic, proceeded always in the direction of chemical equilibrium, and not in the contrary direction by interference of a vital force, as was at that time the more general opinion either openly expressed or vaguely hinted at.

Soon after this, I was able to show a reversible action for one ferment at least, and published the fact in 1898. Meanwhile, the list of intracellular ferments already known was added to by the very important one obtained from yeast by Buchner, the one that induces the alcoholic fermentation of glucose. Buchner's results undoubtedly stimulated the search for intracellular ferments, and now they have been separated in great variety from almost all the tissues of the body and their number is still rapidly increasing. The discovery of new oxidases and peroxidases in various animal and plant tissues, in connexion with the already well-known oxidation processes, is another indication of the leading part taken by ferments in the essential phenomena of life, and it becomes the less surprising that in sympathetic processes also ferments are primarily concerned.

There follows—under the heading of reversibility of enzyme or ferment action—a short account† of such fresh work as I have been able to do on this subject since 1898, and it will be seen that the results then obtained have been confirmed and extended both by myself and by other observers, so that the hypothesis advanced in 1898 that the property of reversible action is common to all ferments seems now to deserve acceptance. The subject of synthesis in the organism will be further discussed after the experimental part has been dealt with, and especially will the chemical equilibrium of the cell or tissue, in health and disease, be touched upon, and certain physiological and pathological modifications of tissues as occurring more particularly in man.

REVERSIBILITY OF ENZYME OR FERMENT ACTION.

In some former experiments communicated to the Chemical Society in 1898¹ I showed that the hydrolysis of maltose to glucose by yeast maltase in concentrated solution was incomplete, and that the phenomenon was due to polymerization of the glucose by a reversible process, so that in solutions of maltose or glucose or of the mixed sugars, synthesis and hydrolysis took place until the system approached a chemical equilibrium, while the point of equilibrium was a function of the concentration of the solution.

In the first stage of polymerization of glucose a large number of isomeric bioses are conceivably possible, but one would expect that with any particular enzyme, or group of enzymes, only those would be formed which are capable of being split back again to glucose by the same enzyme; further, of such substances formed, only those would be found at the end of the reaction which are in equilibrium with the rest when in appreciable concentration, and, the higher the initial concentration of the glucose, the larger might be the number of such substances in appreciable concentration at the end. Again, other conditions equal, an increase in variety of enzyme would increase the total amount of glucose changed.

I have obtained experimental evidence bearing on these points with yeast extract, taka-diastase, and with the enzymes of the pig's pancreas respectively. The products of the synthetic action were not completely identical in these cases. The differences may be due to one or more of the following causes:

1. Specific differences in the enzymes; for example, the maltase of yeast extract being different from that of taka-diastase.

2. Difference in the variety of enzymes present.

3. Difference in the proportion of enzymes present.

So far as concerns yeast extract and taka-diastase, the second and third factors seem to have been chiefly effective.

In every instance, on diluting the products of the synthetic action, it has been possible to split them back to glucose by the enzyme used in their synthesis. Further, the synthetic products of the action with yeast extract were found to be split by taka-diastase, and those of the action with taka-diastase by yeast extract. Preliminary notes on these results were published (taka-diastase and reversed ferment-action;² synthetic action on glucose with pancreatic ferments;³ although it is likely, or at any rate possible, that maltase acting on glucose may produce isomers, it is not proved that, by itself, it can produce anything but maltose, as it has hitherto been impossible to obtain it free from other enzymes.

† A full account will be found in the *Transactions of the Chemical Society* for May, 1903.

In fact, in making a preparation of any enzyme, it is never possible to exclude admixture with unknown enzymes, although particular-known ones may be excluded. That a considerable part of the synthetic product obtained by the action of yeast extract on concentrated glucose solution is possibly formed by the agency of other enzymes than maltase is suggested by fermentation experiments. *Saccharomyces Marxianus* is a yeast which was found by Hansen in 1888 to ferment glucose, but not maltose. I made use of this yeast in 1900 for separating maltose from glucose in mixtures of these two sugars, and published a note on the details of the method.⁴ If the product obtained by the action of yeast extract on concentrated glucose solutions, including thus the synthetic product and the unchanged glucose, is fermented with *S. Marxianus*, only the unchanged glucose is fermented. If, on the other hand, one ferments with a maltase-containing yeast—and I have tried several varieties, each in pure culture—not only is the glucose fermented, but also a part of the synthetic product, the larger part, however, which is not maltose, being unattacked. If, lastly, one treats the product after dilution, first with some yeast extract, similar to that used in its formation, to hydrolyze it, it is then fermented completely by *S. Marxianus*. Evidence has been obtained that the smaller portion of the synthetic product, which is fermented by maltase-containing yeasts, consists of maltose, or partly maltose, and partly higher polymers of maltose. The larger portion, however, which is unfermented unless previously hydrolysed, has optical and reducing properties between those of maltose and those of glucose. It consists mainly of a biose which is not identical with any known sugar, and which I have called "revertose."

The analysis of the product of the action of yeast extract on concentrated glucose solutions was performed by examining the residues left after fermentation of the product (1) with *S. Ellipsoideus* I, (2) with *S. Marxianus*, and subsequent fractionation with alcohol.

The analysis of a series of fractions of the residue after fermentation with *S. Ellipsoideus* I showed that only one sugar remained. This sugar is proved by combustion of its osazone to be a biose, and is the one I have called revertose. The osazone crystallizes in needles, melting at 173° to 174° (corr'd.) It is distinguished from Fischer's isomaltosazone,⁵ which had an

$$[\alpha]_D = + 7^\circ$$

by being optically inactive.

Revertose itself is a hygroscopic sugar, which has only been obtained crystalline by dehydrating the vitreous sugar, either slowly in an exsiccator over lime, sulphuric acid, or anhydrous cupric sulphate, or, on the other hand, by heating *in vacuo*, when it gives up water and assumes a crystalline state; this takes place at 100°, but much more rapidly at 110° or 115° in a glycerine bath. The sugar has not been obtained in detached crystals. It has a sweet taste. Its optical and reducing properties are as follows:

$$[\alpha]_D = + 91.5^\circ \pm 1^\circ \\ R = 47.5$$

Analysis of a series of fractions of the residue after fermentation with *S. Marxianus*, on the other hand, showed that two sugars remained—the one revertose, and the other, fermentable by all maltase-containing yeasts, is a sugar of higher optical activity. It could not be separated completely from revertose, but the fractions in which it preponderated showed optical and other properties which approached those of maltose. The osazone from these fractions, itself fractionated as described in my former paper, yields a fraction crystallizing in plates which resemble those of maltosazone.

There is, therefore, little doubt about its being maltose. It is, perhaps, hardly necessary to point out that the identity of the sugar is not relevant to the question of the reversibility of its formation, because in any case, it can be reconverted to glucose by the same ferment used in its synthesis. It is, however, in accordance with theory for some maltose to be formed when maltase is present, but it is not necessary that there should be sufficient formed and remaining at the end of the reaction to be recognized as such, and it would be quite consistent with the theory for this sugar, which has been found, formed as it is by a strictly reversible process, to be another isomeric biose. There is, however, nothing in any of the tests I have as yet been able to apply, either analytically or by fermentation, by which I can distinguish it from maltose. Not more than about one part of this sugar to about five parts of revertose is formed, but the total amount of

glucose changed in 41 per cent. solution by yeast extract, is nearly one-third of the whole. It is considered also that more maltose is formed in the reaction than appears as such at the end, as part seems to be converted to dextrin by the diastase in the yeast extract.

The question then arises, Is revertose formed by maltase or by another enzyme in the yeast extract? Fermentation experiments, on the one hand, might seem to show that the yeast extract, which is prepared from dried Bern yeast contains an enzyme capable of synthesizing revertose, but not present as such in the fresh maltase-containing yeasts, and therefore distinct from maltase. Another explanation is, however, possible; when maltose is fermented by a maltase-containing yeast, the splitting probably takes place intracellularly. The conditions of equilibrium prevailing within the cell may be much more favourable for the splitting of maltose than for the splitting of revertose; they must be somewhat so, as on comparing the equilibrium of maltose $\rightleftharpoons$ glucose with that of revertose $\rightleftharpoons$ glucose in sugar concentration of 40 per cent., it is seen that the splitting of maltose is much nearer completion; or, looking at it from the synthetic point of view, much less of maltose is formed than of the other biose. The equilibrium of maltose with glucose is the more favourable for hydrolysis, of revertose for synthesis.

The products obtained by the action of taka-diastase on 60 per cent. glucose solutions have not been separated. The quantity of glucose converted is actually greater than appeared when stated in terms of conversion to maltose,¹ as the optical activity and cupric-reducing power of the mixed synthetic products lie between those of maltose and those of glucose. This is true both of the products obtained with yeast extract and with taka-diastase; but in the case of the latter there are also other products not yet investigated, which diminish the optical activity of the total products.

Fermentation experiments with the synthetic product of the taka-diastase action show that, just as with the products of yeast extract, a portion not fermented by *S. Marxianus* is yet fermentable by maltase-containing yeasts, the remainder not being directly fermented even by these. The change observed with pancreatic extract on 60 per cent. glucose solutions was small and probably incomplete on account of destruction of maltase by trypsin. It was verified, however, after subsequent fermentation of the unaltered glucose with *S. Marxianus*.

Since I published my first paper on this subject there have appeared from time to time, besides some small contributions by myself, observations by others of a similar nature, further extending the list of ferments for which a reversible action has been noted. Kastle and Loevenhart found that lipase had a reversible action on ethyl butyrate.⁶ Hanriot also independently observed the reversible action of lipase.⁷ Wroblewski was able to detect a reversible action with invertase, but I have not had the opportunity of seeing his original paper.⁸ O. Emmerling has recorded another synthesis with yeast extract, namely, that of amygdalin from glucose and amygdalo-nitril-glucoside.⁹ Recently, Emil Fischer and E. F. Armstrong have noted the reversible action of kephir-lactase on a new biose, isolactose, which yields glucose and galactose on hydrolysis.¹⁰ And more recently still, Acree and Hinkins have found the hydrolysis of triacetylglucose by pancreatin to be reversible.¹¹ These results, together with my own further results, make it increasingly more probable that the view I put forward in 1898 is a correct one, namely, that all ferment actions are reversible, and warrant, I think, the adoption of such a view as a sound working hypothesis.

THEORETICAL CONSIDERATIONS.

When it was supposed that ferments were concerned only with breaking-down processes it was customary among some writers to speak of the substance which a ferment could break down as its "substratum." Terms are wanted to indicate not only the substances broken down by a given ferment, but also the simpler substance into which the "substratum" is broken down, and on which the same ferment is also capable of acting, but in a synthetic fashion, for they also are a substratum and a ferment works between two strata. I will, for purposes of description, now use the terms ana-products and kata-products, as these will readily be understood to denote the synthetic on the one hand and the broken-down, or split, products on the other.

Ferment action, so long as the ferment is undestroyed and is in the presence of its ana-products or kata-products, never ceases, and only becomes inappreciable when equilibrium between the ana-products and kata-products is sufficiently nearly

approached. If either the ana-products or kata-products are removed from the sphere of action as fast as produced, the other product will be entirely transformed. In this way, as I formerly pointed out,¹ the reversibility of ferment action is sufficient to explain the synthetic processes of life which may, and probably do, occur in stages, so that the ana-products of one ferment are the kata-products of another, the final ana-products usually having a very low solubility. There is thus a series of stages in which the change may be in one direction or the other, but which under ordinary circumstances will be in the same direction for the whole of one series. A unit of living matter must be considered to include many such series, the direction of change varying usually among the several series. The production of isomera by ferments increases their capability for a double rôle in metabolism, for, as has been shown, the equilibrium point of each with the common substances from which they are formed may be different, the one favouring synthesis rather than the other.

The part played by cell membranes and nuclear membranes is no doubt conservative—preventing ferments, zymogens, and other complex substances from diffusing out, while allowing simpler substances to pass both in and out. The equilibrium points of all the intracellular reactions will be constantly changing, depending as they do on the absolute as well as the relative concentrations of the ana-products and kata-products of each, and these in turn dependent not only on the reaction itself, but also on the diffusion rates, and the osmotic relations of the cell and its surroundings. If, for instance, a cell takes up water so that the concentration of its soluble contents is lowered, there will be a general shifting of equilibrium points, so that the velocity of the katabolic changes is increased relatively to that of the anabolic; if, on the contrary, a partial dehydration occurs, the reverse will take place and may result in spore-formation and the like. Yeast in a 1 per cent. solution of glucose or maltose forms very little intracellular glycogen, but in 10 per cent. or 20 per cent. sugar solutions it forms much.¹² But in the higher organisms at least, it is known that the cell equilibrium in health is under the control of the nervous system, though the process by which the metabolism is thus influenced has not yet been made out. It is suggested here, whether electrolysis plays a part or whether something quite different first occurs, that at any rate in the result, water is taken up by the cell or vice-versa, and thus metabolic changes are influenced. It is to be noted that a small change in equilibrium in the direction favouring katabolism may result in the transformation of a minute quantity of a zymogen to a ferment as one reaction, and this may in turn accelerate another reaction out of all proportion to the initial change in equilibrium, for in many reactions, doubtless, the state of equilibrium may already be favourable for change and awaiting only the liberation of free ferment. The atrophy of tissue that follows the cutting off of trophic nerves must be attributed to excess of katabolic over anabolic changes following disturbance of chemical equilibrium.

In a thesis by the author for the M.B. degree, entitled *Nervous Hyperglycaemia*, it was suggested that certain forms of hyperglycaemia which depend on a nervous lesion were to be explained by the alteration of the cell equilibrium, that is, by passage of water into the liver cells, and that such hyperglycaemia, resulting in glycosuria, was to be explained as a paralytic secretion of the liver. Whether the so-called internal secretion of the pancreas acts on the nervous system, or whether it is a ferment resorbed by the liver, I do not wish to discuss, as it is a subject rather for experiment; but with regard to the pathology of alimentary glycosuria, associated with a so-called gouty habit, I would say that in some cases there seems to be a temporary disorder of cell equilibrium depending on circulatory disturbance in the liver, and relieved by salicylates; in others there is probably an actual diminution of the ferments or their zymogens which are necessary for the metabolism of carbohydrates, including the assimilation of sugar. Then as regards senile change in general. In what does it consist? Premature senility can usually be traced to toxic influences, and it is known that tissue poisons are substances which are destructive of ferments. The toxins of disease have not been sufficiently studied from this point of view, but will doubtless follow in the train of alcohol, chloroform, and the other antiseptics, at one time supposed to differentiate between organisms and enzymes, but now shown conclusively to have a destructive action on the latter. By the total destruction of one ferment in a metabolic series, disaster might

befall a cell or tissue unit, or again recovery might be perfect if the zymogen were left intact. Numerous and varying degrees of injury as the result of accident or disease may thus occur, leading to more or less premature senility in a tissue. Physiological senility is probably the slow and gradual diminution of certain of the tissue ferments, and is in accord with the fact that all metabolic changes become slower with advancing age, and so less food can be dealt with in a given time. The peptonizing of nutrient foods may replace the natural process of digestion, but assimilation requires ferments just as much as digestion, and at present this deficiency cannot be made good.

I have spoken of a unit of living matter. If these remarks had applied only to yeast, possibly the word "cell" would have sufficed, but so often the unit is obviously not the cell. In a plasmodium for instance, there are no cells, while in nucleated cells, not even the nucleus in one sense is a unit, for it is not structureless; in another sense not less than the whole organism is a unit, whether it consists of one cell or many. Even in the latter sense and in the highest organisms at one period of life a single cell is the unit, namely, the fertilized ovum, which must contain the parent substances of all the ferments of the fully-developed individual. From the positive results obtained in the direction of artificial parthenogenesis, it seems likely that the female reproductive cell, and perhaps also the male, contain these independently, and yet not in the best proportion until they are averaged by the process of fertilization. Variation amongst the off-spring is to be explained by small variations in the proportions of ferments in the germ-cells, which are characters impressed on these cells and their descendants. In development of the individual, differentiation of the cells takes place from difference in position and surroundings, whereby an "impressed character" is received, and a cell on division always divides into two cells identical with the parent cell, thus are tissues derived (Hertwig.) It is here suggested that the "impressed character," acquired by position or surroundings, is to be explained as a modification of the cell-ferments in number or in proportion. How, then, does reversion to a former type occur? It has been suggested above that variation is due to the modification of ferments in the germ-cells or their descendants and it has also been suggested that complete destruction of a ferment may be recovered from if the zymogen be left; similar recovery would be possible if the zymogen were also destroyed but the pro-zymogen left and so on to the *n*th degree. Reversion may be due to some such recovery from an impressed character at some period of the individual's life-history.

The cells of more embryonic type, that is, cells that have received fewest impressed characters, if included in situations that are not normal to the individual, are a source of danger, as they are at too much advantage for undergoing growth and reproduction as compared with their neighbours, and they often form tumours. Malignancy in neoplasms may be determined to some extent by the two following factors, a comparative freedom from impressed characters on the part of the cells which multiply and form the growth, and a comparative senility on the part of the invaded tissue. But the latter factor often seems very small. It has been suggested that irritation, which sometimes seems a factor in epithelial cancer, may act by injuring the neighbouring tissue or limiting membrane; but perhaps the change is in the first cancer-cell and consists in the introduction or development of a necessary ferment, is in fact the removal of an impressed character. All that is urged on the matter here is that a comparison of the intracellular ferments of a cancerous growth with those of the normal tissues of the type from which such a growth started might lead to useful results.

It is not intended to discuss fully the pathology of those forms of disease that have been mentioned in the foregoing remarks, but merely to indicate the points of contact with my own conclusions based on the special experimental work I have described.

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THE Russian Gynaecological Society will hold its first meeting in St. Petersburg at the beginning of January, 1904.

CASE OF TUBERCULOUS MENINGITIS IN AN ADULT, WITH UNUSUAL SYMPTOMS.

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THE following case is of interest on account of the unusual and misleading nature of the symptoms, together with the fact that the disease ran a very acute course in a patient in whom there was no reason to suspect any primary tuberculous lesion.

CASE.—The patient was a married woman, aged 40, who since 1897 had been under treatment for pelvic trouble, for which she was operated on in November last by Mr. Morse, and an abscess in connexion with the left ovary and tube dissected out. The cause of the pelvic abscess, apparently of old standing, was not obvious, but at the time of the operation there was no reason to suspect a tuberculous origin. The patient's family history was excellent; she herself had nothing about her suggesting either a tuberculous taint or any active or latent tuberculous process. After the operation she put on weight and seemed in excellent health. Mr. Morse was called to see her on January 1st, 1903, and found her suffering from sickness and diarrhoea, ascribed to an error in diet. She quite recovered from this in a day or two, and remained in very good health till January 20th, when Mr. Morse again saw her for severe headache and sickness. The headache was very intense and was not referred to any particular part of the head, at times seeming most severe in the left occipital region, at others referred to the root of the nose as well, and sometimes to the vertex. The sickness occurred about three or four times a day, with no relation to food. This condition remained for a week, during which time the pain in the head became very severe, once waking her thirteen times in one night, and it became necessary to give morphine in order to relieve it. Her pulse during this time was nearly always 64, her normal rate being 70, and her temperature as a rule 97.8°, never rising above normal. Her mind was perfectly clear; she had no paralysis anywhere; the pupils were equal and active, and the knee-jerks normal.

On January 27th it was noticed that she constantly misused and misplaced words, being aware of the fact, as she complained of "being muddled this morning." Thus she ordered her bed to be put on the dressing table, and instead of "be in the end bedroom," she said "be in the bendend-room."

It was thought that possibly the disordered speech might be the result of the morphine, and that a decayed tooth might account for the headache. Gas and ether, which she had had twice previously, was accordingly administered and two teeth removed. Just before taking the anaesthetic she complained of seeing double. After the removal of the teeth she walked back to bed and was quite rational for about an hour, when she suddenly became restless, noisy, her speech was quite incoherent, and she recognized no one.

On January 28th we saw her for the first time in consultation. She was lying curled up in bed on her left side, away from the light, with both hands on her forehead as if in pain, constantly moving about and muttering to herself, unable to recognize any one or understand anything, though she would open her eyes and look at any one when loudly roused. There was no deviation of the eyes, no squint, pupils rather small, equal and active, no paralysis or weakness anywhere; reflexes normal; Kernig's sign absent. Just below each mastoid process she was very tender to pressure. The optic discs were quite normal, and the membrana tympani normal on both sides. There was no discharge from the nose or mouth. Her temperature had risen a degree since the day before, and was now 98.4° in the axilla. Heart and lungs normal.

Dr. Newton Pitt, of Guy's Hospital, saw her in consultation on the evening of January 28th, and agreed that the most probable diagnosis was one of cerebral abscess. He thought she still had some degree of sensory aphasia, for, although it was very difficult to get her to respond to any commands, she would occasionally put out her tongue when told to open her eyes. This, with the fact that she had continually misplaced words on the previous day, made it possible that the seat of the lesion was in the neighbourhood of the left auditory word centre or of the tract connecting it with the frontal lobe, but the localization was too indefinite to warrant an exploratory operation.

On January 29th she remained in much the same condition,