centres are the parts which are especially developed in the brain of man as compared with that of the lower animals.¹¹

It is only fair to Broadbent to point out that more than twenty years previously he had cited almost exactly these regions of the cerebral cortex as parts that were neither in direct relation with peduncular fibres nor with those of the corpus callosum, and that he had attributed to these regions just the same functions as those now assigned to them by Flechsig.¹²

It is, I think, perfectly legitimate to suppose that the annexes to which I have previously referred tend to be developed in the directions above indicated by Broadbent and Flechsig, though how much of these territories they occupy must remain altogether uncertain. It seems also probable there is no sharp line of demarcation between these annexes and the several sensory areas, and that the combined sensory areas together with the annexes are accustomed to be thrown into functional activity more or less simultaneously. Thus the processes of perception and conception, together with revival of linguistic symbols, are probably almost as inseparable in their localisation as they are in their nature and modes of occurrence, and their anatomical substrata must be supposed to occupy a very considerable extent of the cortex of both hemispheres.

A final question now remains for consideration related to this other which we have just been considering. It is this: Where are we to look for the registration and revival of words in the cerebral cortex? Something additional may now be said concerning the sites of the word centres which could not well have been said at an earlier period, and that is, that each of them is probably to be found partly on the confines of its percept centre and partly on that of its related annexe. This supposition is made because some words (especially names of things, persons, and places) are in closest relation with sensory centres; whilst others, such as verbs, adjectives, prepositions, and other parts of speech constituting the framework of language, are in closer relation with conceptual processes. These two modes of functional activity are, as I have said, absolutely inseparable from one another, and therefore the several word centres must be in most intimate relation both with the sensory centres and with their annexes.

If the views above expressed be anything like an approximation to the truth, it may be judged how vain it would be to attempt to base our explanation of any of the different kinds of speech defect upon the supposed existence of some one separate centre for "ideation," "conception," or "naming" which is connected by means of commissures (long enough and separate enough to permit of isolated damage) with sensory centres on the one side and with motor centres on the other. I am pleased to find that the views at which I have arrived on this important subject—while they differ so much from those held by some of the most authoritative writers on speech defects, are nevertheless in very close accord with those formed by one very distinguished writer and thinker on these subjects—namely, the late Dr. James Ross. All that has been set forth above is thoroughly in harmony with the dictum of Max Müller, who says: "Though sensations, percepts, and concepts may be distinguished, they are within our mind one and indivisible. We can never know sensations except as percepts, we can never know of percepts except as incipient concepts."

REFERENCES.

¹These forms of word memory were first definitely stated by me to be purely sensory in papers on the Physiology of Thinking (*Fortnightly Review*, 1869) and on the Muscular Sense (*BRITISH MEDICAL JOURNAL*, April, 1869); and the name "kinæsthetic" was subsequently (*The Brain as an Organ of Mind*, 1880, p. 543) applied to the complex groups of impressions resulting from movements of this or that part of the body. ²Other French writers as well as Ballet attribute to Charcot the doctrine that "le mot n'est pas une unité, mais une complexus" (*Le Langage Intérieur*, 1886, p. 13) because he also dwelt upon these four different kinds of word memory. Charcot's lectures on Aphasia were delivered in 1883, but M. Ballet will find a full description of these four different kinds of word memory in my book *The Brain as an Organ of Mind*, 1880, p. 696, or in the French translation (*Le Cerveau et la Pensée*, tome ii, p. 222), published in 1882. ³*Brain*, April, 1887, and April, 1892. ⁴*The Brain as an Organ of Mind*, 1880, p. 599. ⁵*Le Langage Intérieur*, 1886, p. 55. ⁶*On Aphasia*, 1887, p. 114. ⁷*De l'Aphasie*, 1885, p. 49. ⁸*Principles of Psychology*, vol. i, 1870, p. 187. ⁹*Inquiries into Human Faculty*, 1883, p. 83. ¹⁰On this subject many interesting details have been given by Ballet, *loc. cit.*, pp. 17-45. ¹¹*Loc. cit.*, p. 48. ¹²In the case of a deaf and dumb child taught to speak and understand others by means of hand and finger movements their thought

counters would be combined visual and kinæsthetic impressions, or in the case of one who had been taught to read much from early life they might be "visual typographic images." On the other hand, in the case of a congenitally blind person who has been taught to read aloud by means of raised letters and words excitation of the centres for touch and kinæsthesia would constitute the initial processes in the act of reading aloud, although revived auditory impressions might constitute, as in ordinary persons, their habitual thought counters. A patient of the former class, whose history has been reported by E. Fournier (*Essai de Psychologie*, Part II, chap. v), says: "Je sens quand je pense que mes doigts agissent, bien qu'ils soient immobiles. Je vois intérieurement l'image que produit le mouvement de mes doigts." ¹³*The Brain as an Organ of Mind*, p. 176. ¹⁴According to Seguin, out of 266 cases of aphasia, he found 243 with right and 17 with left hemiplegia; that is, somewhere about 6 per cent. W. Ogle, on the other hand, from inquiries among 2,000 hospital patients, found that 85 of them were left-handed; that is, about 4 per cent. Left-handedness, curiously enough, was found to be "twice as common in men as in women." He shows, too, how very frequently there is hereditary transmission of this peculiarity. ¹⁵*Guy's Hospital Reports*, xvi, 1871. ¹⁶*Med. Chir. Trans.*, 1871. ¹⁷*Journal of Mental Science*, pp. 28, 32. ¹⁸*Med. Chir. Trans.*, 1871, p. 294. ¹⁹*British and Foreign Medical-Chirurgical Review*, 1886, p. 481. ²⁰Moxon's paper is, indeed, in other respects remarkable, looking to the date at which it was written. Thus, he speaks of spoken words as represented in Broca's region by "educated associations of movements," and the meaning that he attaches to this phrase is rendered evident further on when he dwells upon the "inconceivable pitch of education which is given to these supramotory departments, if I may so call them, of the brain, which hold ready for use the memorial forms of outgoing words," or still better where he says, "the situation of the ideas of associated motions which forms the faculty of speech is supramotory, whilst the situation of the ideas of associated sensations, which form the faculty of language comprehension, is suprasensory." ²¹*Med.-Chir. Trans.*, 1872, pp. 180, 181, and 191. ²²On the Muscular Sense and the Physiology of Thinking, *BRITISH MEDICAL JOURNAL*, May, 1869. ²³*Brain*, i, 1878. ²⁴*BRITISH MEDICAL JOURNAL*, May, 1869. ²⁵*Ziemssen's Cyclopædia*, vol. xiv, p. 779. ²⁶*Le Progrès Médical*, 1883. ²⁷*De l'Aphasie*, 1885, p. 45. ²⁸*Le Langage Intérieur*, 1886. ²⁹*Leçons de Clinique Médicale*, 1896 (Montpellier). ³⁰*Brain*, 1885. The reader will find several of the diagrams previously referred to in an article on the Sensory Side of Aphasia, by E. A. Shaw, in *Brain*, 1893, p. 492. ³¹*Loc. cit.*, p. 477. ³²I shall later on state what I believe to be the interpretation of his seven types of speech defect, when it will be seen that they may be explained without any necessity for supposing the existence of lesions in any such parts. ³³*The Brain as an Organ of Mind*, p. 636. ³⁴*BRITISH MEDICAL JOURNAL*, November, 1887. ³⁵*Le Progrès Médical*, March 21st, 1885. ³⁶*On Aphasia*, 1887, p. 123. ³⁷*Brain*, 1889, p. 97, where Starr says: "The results of pathological observation fail to give any support to the hypothesis of an 'ideational centre,' which Broadbent and Kussmaul have introduced into the diagrams." ³⁸*The Disorders of Speech*, 1894, pp. 230 and 235. Wyllie, however, I think, tends to convey an erroneous impression by representing in a diagram on p. 276 of his work the seats of word revival in a lower plane and of percept revival in a higher plane, and assuming that the stimulation of Broca's centre takes place from the seat of percept revival rather than from the auditory word centre. This seems to be also the position of Lichtheim, judging from his Fig. 7, and what he says in reference thereto, *loc. cit.*, p. 477. ³⁹Examples will be given later, when speaking of the defects due to disabilities in the auditory word centre. ⁴⁰*Neurol. Cent.*, 1894, pp. 674 and 809; and *Gehirn und Seele*, Leipzig, 1895. ⁴¹Since the above was written I have received from Déjerine the reprint of a communication made by him to the Société de Biologie, on February 21st, 1897, in which he contests these views of Flechsig. ⁴²*Med.-Chir. Trans.*, 1872, p. 178.

THE GOULSTONIAN LECTURES

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CHEMISTRY AND PATHOLOGY OF GOUT.

Delivered before the Royal College of Physicians, March, 1897.

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[ABSTRACT.]

LECTURE II.

THE SOURCES AND FORMATION OF URIC ACID IN PATHOLOGICAL CONDITIONS, OTHER THAN GOUT, IN WHICH IT APPEARS IN THE BLOOD.

ALTHOUGH I hold the opinion that in health uric acid is only formed in the kidneys, and that the uric acid found in the blood in gout is absorbed from the kidneys after formation in those organs, yet it must be borne in mind that there are other diseases besides gout in which uric acid appears in the blood, and in connection with which it has most probably not been absorbed from the kidneys, but has been formed elsewhere in the system.

Blood Disorders accompanied by the Presence of Uric Acid in the Blood.—Von Jaksch¹ found uric acid in the blood of cases of primary and secondary anæmia, of pernicious anæmia and of splenic tumour, also in conditions inducing dyspnoea such as heart disease, pleurisy with effusion, pulmonary catarrh, pneumonia, and emphysema. Klemperer has confirmed this, and Laache,² Bartels, and others have shown that the

presence of uric acid in these patients' blood is associated with a great increase in the amount excreted in the urine. Von Jaksch concluded that the uric acid in the blood resulted from diminution of the oxidising activity of the red corpuscles which leads normally to the destruction of the uric acid formed in the body. Horbaczewski's view that the acid arises from leucocyte disintegration would equally fit the facts, particularly when it is remembered that experimental evidence shows that the process of oxygenation can in the presence of nuclein produce uric acid instead of destroying it.

Renal Diseases accompanied by the Presence of Uric Acid in the Blood.—Von Jaksch³ found uric acid in the blood of all the cases of renal disease that he examined, the proportions being especially large in cases of granular kidney disease and uræmia. Von Jaksch's⁴ results were confirmed by Klemperer, who examined the blood of cases of contracted kidney, and found uric acid always present in the blood.

Lead Poisoning accompanied by the Presence of Uric Acid in the Blood.—Sir Alfred Garrod⁵ examined the blood of nine patients suffering from plumbism, and who had never suffered from gout, and found appreciable quantities of uric acid in the blood of seven out of the nine. This is no doubt due mainly to the kidney condition, though the increased leucocytosis may possibly play some part in it.

Fever and Absence of Uric Acid in the Blood.—Von Jaksch found no uric acid in the blood of patients suffering from typhoid fever, intermittent fever, and acute rheumatism, nor in connection with the diseases of the liver, stomach, and intestines, when accompanied by anæmia. His observations seem undoubtedly to prove that the presence of uric acid in the blood is not a factor in the production of the so-called uric acid intoxication of fever. Fever, indeed, appears to influence unfavourably the production of uric acid.

A proposition that I wish to put forward is that the seat or site of formation of uric acid is a different one in gout to what it is in those blood diseases and disorders in which uric acid occurs in the blood without the development of gout. In gout I believe that all the uric acid present in the blood is absorbed from the kidneys, owing to some affection of those organs—functional or organic—which interferes with the proper excretion of the uric acid manufactured in the kidneys. In cases of contracted granular kidney disease, and in cases of plumbism, the uric acid present in the blood is, I believe, derived from the same source—namely, from the damaged kidneys. In blood diseases and disorders the uric acid present in the blood is probably derived from the nuclein of the leucocytes, and, as the kidneys are in a sound condition, it is readily excreted by them.

An interesting question which I will now consider is whether gout ever occurs without preceding kidney mischief of some kind or other.

ASSOCIATION OF KIDNEY AFFECTIONS WITH GOUT.

In the first place I think that the old idea must be abandoned that the kidneys can only eliminate a certain amount of uric acid. That the healthy kidneys are capable of separating from the blood and excreting large quantities of uric acid is shown by the observations previously referred to.

Views as to the Association of Gout and Kidney Disease.—Sir Alfred Garrod, Sir William Roberts, and Levison all attribute the accumulation of uric acid in the blood of gouty persons to deficient excretion rather than to increased production. Vogel⁶ estimated, in three cases of chronic gout, the intake of nitrogen by analysis of the food and the output of nitrogen in the urine and feces. He found that there was a nitrogen retention greatly in excess of what could be attributed to a retention of uric acid. Vogel states that his patients behaved in this respect like sufferers from renal disease, although the clinical signs of granular kidney mischief were wanting in all the cases. It must be borne in mind that the absence of the clinical signs of kidney disease does not necessarily imply integrity of those organs.

Association of Renal Disease with the Presence of Uric Acid in the Blood and with Uratic Deposits in the Joints.—As previously mentioned, Von Jaksch found considerable quantities of uric acid in the blood of all the cases of diseases of the kidneys that he examined, and his results were confirmed by Klemperer. Drs. Ord and Greenfield⁷ found uratic deposits in the

joints of a considerable proportion of patients suffering from kidney disease, and their results have been confirmed and extended by Dr. Norman Moore.⁸ Levison states that all the *post-mortem* examinations of patients dying of granular kidney disease at the Communal Hospital, Copenhagen, during a period of fourteen months showed uratic deposits in one or other of the joints, although most of the patients are not known to have had any gouty definite attack. By the kindness of Dr. Cyril Ogle, Dr. F. J. Smith, Dr. Hebb, and Mr. Jackson Clarke I am able to give the results of seventy-seven similar examinations made in London hospitals.

	No. of Cases.	Uratic Deposit in Joint or Joints.
Known to have had gout	10	10
Never known to have had gout	67	31
Totals	77	41

If from the 67 cases a selection is made of those described as "markedly granular" or as "typical granular kidneys," then the proportion of cases in which uratic deposits were found in the joints appears as follows:

	No. of Cases.	Uratic Deposit in Joint or Joints.
Marked granular kidney disease ...	26	20

Thus it is seen that among the cases of marked granular disease of the kidneys occurring in persons who were never known to have suffered from ostensible gout during life, uratic deposits were found in the joints of 77 per cent. of the cases.

It has been urged that, if kidney disease, with the consequent diminished excretion of uric acid, be the primary factor in the causation of gout, signs of kidney mischief would always manifest themselves prior to an attack of gout, and that very few such cases have ever been recorded. But, in the first place, it must be remembered that such signs are not usually looked for, and, in the second place, they need not necessarily reveal themselves clinically. It is well known that contracted granular kidney is not always evidenced either by the occurrence of albuminuria or of dropsy.

The contention that, if organic renal failure existed, the urea excretion would probably be equally affected together with that of uric acid, does not hold good if the view is adopted that uric acid is produced in the kidneys while urea is only eliminated by them.

Kidney Disease and Gout alike caused by certain Toxic Agents.—Certain toxic agents which predispose to or which excite kidney disease are also known to produce gout. Lead gives rise to both chronic kidney disease and gout. In chronic lead poisoning proliferation of the epithelium of the urinary tubules first occurs, followed by granular atrophy and excessive formation of interstitial tissue. Very similar changes occur in the gouty kidney, and it seems reasonable to assume that the changes in that organ in both chronic lead poisoning and in gout so affect the excreting apparatus of the kidneys as to seriously diminish their power of eliminating uric acid.

Sir Alfred Garrod has shown that lead poisoning leads to the accumulation of uric acid in the blood. He also found that the medicinal administration of lead acetate caused the amount of uric acid in the urine to diminish.

Alcohol is another body which in excessive quantities gives rise to kidney mischief, and which may also give rise to gout.

Probable Anatomical Seat of the Kidney Affection causing Gout.—The anatomical seat of the presumed kidney affection giving rise to the development of gout is probably in the epithelium of the convoluted tubes, as that has been shown by Levison⁹ to be the primary seat of disease in granular kidney, and by Oliver¹⁰ to be the seat of the kidney affection associated with lead poisoning. The increase of interstitial tissue is probably a secondary change.

My own belief is that a functional affection of the kidneys always precedes any gouty manifestations, and that this functional affection may subside if the exciting cause be removed, or it may pass on to a structural lesion. It is the liability to this functional affection of the kidneys which, in my opinion, constitutes the hereditary factor of gout. If this view be correct, it is obvious that the kidney condition must always be considered in the treatment of gout, and that given diseased organs incapable of eliminating the normal amount of uric acid, either some other channel for its elimination must be secured, or its formation must be limited to the diminished output, so that absorption of it into the general circulation may be avoided.

The retention of uric acid in certain cells of the kidney, and its subsequent absorption into the blood, is analogous, as Sir Alfred Garrod has pointed out, to an attack of jaundice. When no obstruction exists to the exit of bile from the biliary passages, no appreciable amount of its colouring matter is found in the blood, but when its free elimination is checked, then absorption of it into the blood speedily takes place.

ORIGIN OF URIC ACID.

I now propose to review the theories which have been put forward as to the origin and antecedents of uric acid and the chemical processes by which it is formed. A commonly received notion is that uric acid represents a less complete oxidation of the nitrogenous constituents of the tissues than does urea; this is based on the facts that urea can be obtained as an oxidation product of uric acid, and that in certain reptiles in whom respiration is languid and the temperature low, uric acid is excreted and no urea. But birds, in whom respiration is more rapid and the temperature higher than in mammals, also excrete practically pure uric acid.

Another common view is that in gout there is an excessive formation of uric acid due to a too highly nitrogenous diet, and especially to an animal one. But Virchow has often found gout in poorly nourished convicts, while birds fed entirely on grain may develop uratic deposits around the joints, while on the other hand uric acid is absent from the urine of some of the carnivora. Furthermore, Bleibtreu's experiments, confirmed by Hirschfeld, show that although the increased ingestion of nitrogen leads to an augmented excretion of uric acid, it is immaterial whether the proteids taken in be animal or vegetable.

That the production of uric acid is not dependent, at all events to any great extent, on diet is also shown by the fact that the same diet which in one class of animals will produce uric acid will in another class produce urea. Thus in the urine of the carnivorous lion and tiger there is a quantity of urea, and but very little uric acid, on the other hand the carnivorous python and boa excrete uric acid and no urea. Graminivorous birds excrete uric acid and no urea; whilst herbivorous mammals excrete quantities of urea and but little or no uric acid.

Sir William Roberts,¹¹ comparing the functions of the kidneys of birds and serpents with those of mammals, considers that an immense functional evolution has taken place in the mammalian kidney; that the evolution of mammalian urine has probably turned mainly on the point that the mammalian plan required that the renal excretion should be voided, not in the solid or semi-solid form, but as a watery solution. This modification would require the discarding of the sparingly soluble uric acid as a medium for the elimination of nitrogen and the substitution of a nitrogenous substance readily soluble in water, such as urea. He considers it possible that the reason why this substitution has not been completely effected is that in that particular the mammalian type has not yet reached its ideal perfection, and that the residuum of uric acid in mammalian urine may be something in the nature of a vestigial feature.

View that Uric Acid is Formed from Urea in the Kidneys.—In mammalia, including man, and in birds, uric acid is absent from the blood in health, while urea is always present in the blood. The blood of the renal artery is much richer in urea than the blood of the renal vein.

One very strong argument against the formation of uric acid in the liver, spleen, connective tissues, etc., is that it is never present in the blood of mammals (including man) and

of birds in health. If it were formed in such organs or tissues it must be conveyed in the blood to the kidneys. Since, according to Sir Alfred Garrod's and my own investigations, urea, and not uric acid, is found in the blood of birds, and since uric acid, and not urea, is found in the urinary excrement of birds, it seems highly probable that urea is at least one of the sources of formation of uric acid, and that the change is effected in the kidneys.

Dr. P. W. Latham's¹² explanation of the formation of uric acid in the animal economy is that the amido bodies—glycocine, taurine, leucine, and tyrosine—are normally converted in the liver into urea, but if from any cause the metabolism of glycocine be interrupted, there would then be present in the liver glycocine and urea, which would produce hydantoic acid and then hydantoin, and the latter, which is freely soluble, would then pass on in the circulation to unite in the kidneys with urea or with biurate to form an ammonium salt of uric acid. Therefore, according to this view, the imperfect metabolism of glycocine is the primary and essential defect in connection with the abnormal formation of uric acid in the human system.

The production of uric acid from urea and glycocine may be shown in a single equation as follows:

Horbaczewski produced uric acid by the interaction of urea and glycocine, and this result was confirmed by Dr. Latham.

Glycocine is certainly formed in the human body, and probably is one of the antecedents of urea, for in man glycocholic acid, a compound of glycerine and cholic acid, passes in the bile into the intestines, and having served its purpose, and its constituents having been set free, the glycocine, together with the other amido bodies—taurine, leucine, and tyrosine—pass in the portal blood to the liver, and probably, in the hepatic cells are converted into urea.

That glycocine is concerned in the production of uric acid is somewhat probable from the fact that in the carnivora, whose urine contains little or no uric acid, the bile contains no glycocholic, but only taurocholic acid, and therefore yields no glycocine.

It is quite possible that there is another means by which uric acid may be formed from urea. Gerard¹³ has succeeded in converting uric acid into urea by the agency of micro-organisms derived from the air, and Magnier de la Source has effected a similar conversion by purely chemical agencies. The reaction is one of hydration, the uric acid uniting with the elements of water, and yielding urea and tartaric acid, as shown in the following equation:

We may therefore conclude that the conversion of urea into uric acid by the agency of certain of the kidney cells is at least possible, either by the conjugation of urea and glycocine, or by the interaction of urea and tartaric acid, the last-mentioned body being possibly derived from lactic acid.

Uric Acid Formation and Liver Disease.—If uric acid be formed in the kidneys from urea and glycocine brought from the liver, it can be readily understood that alterations in the metabolism of the liver must necessarily affect the formation and excretion of uric acid. This would explain why liver trouble of some kind or another is so commonly associated with gouty dyspepsia, and it also renders intelligible the fact that several observers—for example, Dr. Murchison, Dr. George Harley, and Sir Dyce Duckworth—have been unable to dissociate the connection between liver troubles and gout, and have therefore attributed the formation of uric acid to the liver.

View that Uric Acid is formed from Nuclein.—Horbaczewski¹⁴ has shown that uric acid, as well as xanthin and hypoxanthin, can be prepared from spleen pulp. By digesting fresh spleen pulp with hot water till changes set up by bacterial agency are started, he found that the fluid, when freed from albuminous bodies, contained xanthin and hypoxanthin, but no uric acid. By treating this fluid with arterial blood, and keeping the mixture at 40° to 50° C., uric acid forms in it after several hours.

Horbaczewski found that the nitrogen contained in the uric acid so formed was about equal in amount to the nitrogen

contained in the xanthin and hypoxanthin (xanthin bases). Horbaczewski brings forward proof that the substance which yields xanthin bases and uric acid is the nuclein of the spleen cells. It was found that when pure nuclein, prepared from spleen pulp, was dissolved in very weak alkali, and digested with blood at 40° C., uric acid was formed. The question as to whether a similar decomposition occurs in the blood of ordinary human beings has been solved by the administration of nuclein, which Horbaczewski finds to increase the excretion of uric acid; similar results have been obtained by Umber¹⁵ by giving thymus, liver, and other organs as food.

From his experiments Horbaczewski concludes that uric acid is formed in health by the disintegration of nuclein, and that sudden variations in uric acid production may be due to the breaking up of leucocytes and conversion of their nuclein into uric acid or xanthin bases within the system. It is well known that permanent or temporary leucocytosis—even that following on an ordinary meal—is accompanied by increased uric acid excretion, and Gumprecht¹⁶ further confirms Horbaczewski's views by showing that in those exceptional cases of leucocythæmia in which the excretion of uric acid is normal or lessened, that of alloxur bases (that is, those containing an alloxan and a urea nucleus) is correspondingly increased. But although I think that in such cases, where uric acid is present in the blood, it is probably derived from leucocytic nuclein, it is in my opinion wrong to draw the further inference that the source of the uric acid excreted in health is the nuclein derived from leucocytes throughout the body. If such were the case uric acid would be found in the blood in health; but, as previously shown, it is not. Moreover, in birds there is no special leucocytosis to account for the large formation and excretion of uric acid that occurs.

View that part of the Uric Acid is Introduced Ready-formed in Food.—Dr. Haig, who, in my opinion, wrongly ascribes to uric acid an almost universal rôle in the causation of disease, claims that the uric acid excreted in the urine comes from two sources: 1. The uric acid which is formed in the body out of nitrogenous food. 2. The uric acid introduced into the body ready formed in certain articles of diet, such as meat, meat extracts, soup, tea, coffee, etc. He considered that flesh diet increases both the introduction and the formation of uric acid, a view which is opposed to the previously quoted experimental results obtained by Bleibtren, and by Hirschfeld.

As far as I can ascertain from Dr. Haig's writings he has never identified by the murexid test this uric acid reported to be present in these various articles of diet. Apparently these estimates depend solely on the application of Haycraft's process to the articles of diet, and the subsequent calculation of the silver precipitate so obtained in terms of uric acid. That Dr. Haig's peculiar view as to the direct introduction of uric acid in articles of diet is an error is shown by the absence of uric acid from the blood of man and animals in health. Dr. Haig has also advanced the theory that normally there is a constant ratio of 1 to 35 between the uric acid and urea formation, and that if the uric acid excretion falls below this ratio, it is due to the reaction and storage of uric acid in the liver, spleen, kidneys, joints, and fibrous tissues, whereas an increase in the proportion of uric acid to urea is due to the washing out from its storage places of the deposited uric acid.

This theory of the existence of a normal ratio of uric acid to urea and of every departure from it being due to a pathological cause is disproved by the following experiments:

1. Bleibtren and Schultze,¹⁷ experimenting on themselves, showed that the ratio between uric acid and urea can be considerably altered by means of the diet without the general health being influenced.

2. Dr. Herringham and Mr. Groves,¹⁸ as the result of a series of experiments that they made, entirely fail to corroborate Dr. Haig's observations, and think that either what was true for his system was not true for theirs, or that Dr. Haig's results were, to quote their own words, "inaccurate and deceptive owing to his having employed a very uncertain and inaccurate method for the estimation of uric acid."

3. The results of the determinations that I have made of the total daily eliminations of uric acid and urea in the urine of a healthy adult man, and which consist of observations extending over a period of fifty days, show that the ratio of

uric acid to urea varied from 1:28 to 1:55 (the average being 1:42), although throughout the entire period the individual remained in good health.

These results show that no constant ratio exists between the excretion of uric acid and urea in any given individuals. Variations in the diurnal elimination of the former cannot be due to its being washed out from various tissues and organs into the blood, for it is never found in the blood of healthy persons. They depend, probably, on the amount of glycocine leaving the liver and passing into the kidneys, which in itself may be influenced by diet, exercise, and the nervous system. Dr. Latham¹⁹ states that insufficient exercise tends to the formation of glycocine; thus, horses put to hard work eliminate benzoic acid, while those kept in the stable excrete glycocine compound hippuric acid.

Different Modes of Formation of Uric Acid in Health and in Blood Disorders.—From a consideration of the various views as to the origin of uric acid, I think it is evident that there are two distinct and different ways in which it may originate: (1) In health I believe that it is only formed in the kidneys, probably from urea and glycocine, and that it is at once eliminated in the urine. If from any functional or organic affection of the uric-acid-eliminating cells of the kidneys its proper secretion is inhibited, then it is absorbed into the general circulation, and constitutes the store from which the uratic deposits of gout are formed. (2) In diseases which are accompanied by leucocytosis, I believe that uric acid may be formed from the nuclein of leucocytes in the spleen and possibly throughout the system generally, but that such uric acid is readily eliminated by the kidneys which remain sound as regards their uric acid secreting structures; consequently, gouty deposits never occur in connection with such diseases.

CAUSES OF URATIC DEPOSITION IN GOUT.

Form in which Uric Acid exists in the Circulation.—Sir William Roberts²⁰ has shown that the amorphous urate deposit of human urine is of the same composition as the solid, or semi-solid, urinary excrement of birds and serpents, the only difference being one of physical form. Dr. Bence Jones²¹ was the first to show that the amorphous urate deposit yielded to water a soluble moiety consisting of true biurate, and left a sediment consisting of pure uric acid, and from the results of his analyses he inferred that the amorphous urate deposit consisted of, or at least often contained, a molecule of biurate in loose combination, with a further molecule of uric acid. Sir William Roberts took up and continued the investigation dropped by Dr. Bence Jones thirty years before, and has conclusively shown that a third order of uric acid salts—the quadriurates—exists, and that the amorphous urate deposit of human urine, and the urinary excretion of birds and serpents, belong to this order, and consist of a true and definite compound of biurate and uric acid in the proportion of one molecule of each. Sir William Roberts concludes that the quadriurates are the physiological combinations of uric acid.

As I have been unable to ascertain that any quantitative determination of the bases present in the amorphous deposit has been made, I investigated this point in the following manner:

Several gallons of acid urine from febrile patients were taken, and the precipitate collected on a filter, decomposed by boiling with excess of HCl, and again filtered and evaporated to dryness. The residue, containing the bases as chlorides, was taken up with distilled water, filtered, and again evaporated to dryness. Part of the residue was analysed qualitatively, and found to consist of ammonium, sodium, and potassium, with minute traces of calcium and magnesium. In the remainder the amounts of the first three bases were estimated and found to be, in percentages—ammonium 46, sodium 40, potassium 14, corresponding to 7, 5, and 1 molecules of their respective quadriurates.

The uric acid which is formed in the kidneys is probably at once converted into the mixture of these three quadriurates, which in the normal state are then excreted, dissolved in the urine. If, however, any absorption of them takes place into the blood, as probably occurs in the gouty state, the ammonium and potassium quadriurates would be converted by the sodium carbonate of the blood into sodium quadriurate, which would constitute the sole compound of uric acid circulating in the blood. It is from this body that the sodium biurate, of which the gouty deposits consist, is formed.

Formation of the Sodium Biurate from the Quadriurate.—Sir William Roberts investigated the behaviour of uric acid

with blood serum and with a standard solvent containing 0.5 gr. sodium chloride, and 0.2 gr. sodium bicarbonate in 100 c.c.m. of distilled water. He found that each, at the temperature of the body, dissolved 1 part in 500 of uric acid, sodium biurate being only about one-twentieth as soluble. The chemical action involved is the conversion of the uric acid into quadriurate by the sodium carbonate present, the excess of which effects a further conversion into biurate, which, on account of its less solubility, is eventually precipitated.

Sir William Roberts infers from these results that, in the normal state, uric acid is primarily taken up in the system as quadriurate, and that as such it circulates in the blood. The detained quadriurate, circulating in a medium rich in sodium carbonate, is gradually transformed by the latter into sodium biurate, and as this form is almost insoluble, precipitation of it occurs or is likely to occur.

The reason that in leucocythæmia and other blood diseases no uratic deposits occur is that the uric acid produced in the various organs or tissues is discharged into the blood as a quadriurate; and as this requires some hours for its maturation before it is possible for it to deposit sodium biurate, there is abundant time for the kidneys to eliminate it provided these organs are sound. In connection with gout, if the view is correct that defective elimination of uric acid by the kidneys always occurs, the conditions are quite different.

SEATS OF URATIC DEPOSITS IN GOUT.

Uratic deposits are found almost exclusively in structures belonging to the connective-tissue class—in cartilages, ligaments, tendons, and in the cutaneous and subcutaneous connective tissue. They are conspicuously absent from the muscular tissue and from the substance of the liver, spleen, brain, and lungs. Uratic deposits have been very occasionally found in the following places: In the mitral and aortic cardiac valves, in atheromatous patches in the aorta, in the walls of veins, in the crico-arytenoid ligaments, in the vocal cords, in the walls of bronchial tubes, in the mucous follicles of the pharynx, upon the meninges of the brain and spinal cord, upon the spinal nerve sheaths, in the sclerotic coat of the eye, and the fibrous envelope of the retina. It is always in the fibrous tissue which participates in the formation of the nervous envelopes that the deposit is found.

Anatomical Seat of the Deposit in Cartilages.—The uratic deposit first occurs in the central portion of articular cartilage—a point farthest from the network of nutrient capillaries and a point where nutrition is more easily retarded. It is also probably the point of greatest pressure, hence a long walk, a dance, or similar violent exercise may precipitate an attack of gout.

Ebstein states, as the result of the examination of a typical gouty knee-joint, that directly under the surface of the cartilage a very shallow tissue layer exists in which crystals are wanting, and in the layer immediately beneath this the crystals are most plentiful. He agrees with Sir Alfred Garrod that only two-thirds of the thickness of the cartilage is usually infiltrated, although exceptionally—as shown by Cornil and Ranvier—the whole cartilage may be infiltrated.

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- ¹⁶ *Centralblatt für allgem. Path. u. path. Anat.*, 1896, vii, p. 820. ¹⁷ *Pflüger's Archiv*, Band xlv, p. 401. ¹⁸ *Journal of Physiology*, 1891. ¹⁹ *On the Formation of Uric Acid in Animals*, 1884, p. 42. ²⁰ *Croonian Lectures on Uric Acid Gravel and Gout*, 1892. ²¹ *Journal of Chemical Society*, 1862, xx, p. 201.

An effort is being made throughout the country to raise a children's tribute towards the Queen's Commemoration Fund for the Queen's Jubilee nurses. The fund has already reached the sum of £30,000. A lecture entitled "The Children's Story of the Queen's Reign" will be given in the chief provincial towns. The Duke of Westminster has given the use of Grosvenor House for the first lecture on Monday, March 29th.

AUDITORY APHASIA WITH AMUSIA.

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BEFORE entering upon a description of the case which is the subject of my paper, I think it advisable, for the better comprehension of what is to follow, to refer briefly to some points in connection with auditory aphasia.

Auditory aphasia—more commonly known as word deafness—includes those disorders of hearing and speech which result from destruction, partial or complete, of the posterior half of the first temporal convolution on the left side. This convolution is the storehouse for the sound images of words, and hence, when it is destroyed, the power of understanding spoken language is lost. The patient is not deaf—he hears quite well, but he fails to understand. He hears language as sounds, but he cannot comprehend their meaning. He is in the position of a man listening to an unknown tongue; he hears the sounds of the spoken voice, but he is unable to interpret their significance.

But auditory aphasia may include something more than word deafness. Not only does the patient fail to comprehend spoken language, but he may have lost the power of producing language. The word storehouse is destroyed or isolated, and he cannot therefore reproduce in the form of spoken language the thoughts that arise in his mind; he has, so to speak, forgotten how to speak, and his attempts at speech merely result in the emission of an unintelligible jargon, "gibberish aphasia," or, short of this, in efforts which reveal a very greatly diminished vocabulary, and a failure to recognise the true meaning of the words to which he gives utterance.

Agraphia is frequently present, but though the patient cannot write, just as he cannot speak, yet he may copy what is placed before him, for he generally comprehends word symbols—that is, he is not word blind.

Occasionally the musical faculty, which seems to reside in the left first temporal convolution, is lost or sensibly impaired.

In auditory aphasia, then, there may be defects in the reception or interpretation as well as in the production of spoken language, and agraphia and amusia—musical aphasia—may coexist.

DESCRIPTION OF CASE.

The patient, a man aged 51, by occupation a seaman, was admitted under my care in the Aberdeen Royal Infirmary on March 19th, 1895. His history, obtained mainly from his wife, was as follows: For some years back he had suffered from breathlessness and palpitation of the heart, and a year ago he became so breathless and ill that he sought admission into the Aberdeen Royal Infirmary. During his stay in hospital (he was not then under my care) his symptoms pointed to cardiac weakness, for the heart's action was feeble and irregular, the sounds were faint but free from murmur, and there was much cyanosis and dyspnoea. After a short stay in the infirmary he was discharged greatly improved, and he soon resumed his occupation as a sailor. He continued in fair health until February 11th, 1895, when, on the afternoon of that day, while at sea, he suddenly became dazed and stupid, and found that he could not understand what was said to him. He remained in this condition for several days, during which it was discovered that he could neither read nor write. He often attempted to read, but it was evident that his efforts were fruitless, for he was frequently observed to be puzzling over a book or newspaper, which he held as often as not upside down in his hands. He rarely spoke, and when he did speak his language was at times not at all intelligible. After a few days the power of writing and of reading (silently as well as aloud) was restored, and voluntary speech returned to a considerable extent, but no improvement was manifested in his hearing. At no time of his illness did he lose consciousness, nor was there ever any evidence of paralysis.

On admission his expression resembled that of a deaf man, but he was not deaf, for if asked (in writing) whether he heard conversation he stated that he heard a sound, but that he did not understand what was being said. At the same time he was not absolutely word deaf, for when requested to