REMARKS ON SOME POINTS OF INTEREST IN REGARD TO THE PRESENCE OF SUGAR IN THE URINE.

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A FEW years ago I published in the *St. Thomas's Hospital Reports*, vol. xii, some notes on glycosuria, chiefly as observed in persons who had passed the middle age of life. The observations then recorded have been followed up and added to, and I now venture to set before you some statements and remarks in the way of supplement and illustration. These statements and remarks must not be taken to represent final decision in any one direction. They are, on the contrary, presented as matters to be thought about, matters which, being amplified by further note and thought, may help us to understand more of what indications in the way of diagnosis and treatment may be drawn from the occurrence, in one case or another, of glycosuria.

I trust that I shall not weary you if I review, in the outset, the conditions which may, so far as our knowledge goes, determine the presence of sugar in the urine in pathological quantity. Summarised as briefly as possible the conditions are: 1, excessive afflux of arterial blood to the liver, and probably to other glyco-genic organs; 2, defective assimilation of glucose; 3, defective formation of glycogen; 4, instability of glycogen, namely, the formation of glycogen which is too easily transformed; 5, excessive ingestion of glucose or glucose-yielding substances.

Under the first head may be gathered several kinds of cause; for example, 1, vasomotor paralysis, determined by disease or injury of the medullary centre or of the nerves connecting the centre with the arteries of the liver; 2, dilatation of the hepatic artery, not determined by disease of nerve centre or nerves, but by irritation in the liver, or by reflex action at the instigation of other organs, such as the stomach, or by general disorder of the circulation, functional, a result of nerve strain or excitement, functional and probably also dyscrasic, as in gout; 3, possibly also compensatory hyperæmia, balancing obstruction of the arterial circulation in other parts and systems of the body. So far as I know, this possibility has not been hitherto discussed. But the converse of it appears to be pretty clearly established by actual experiment. Dr. Lauder Brunton, in the *Handbook for the Physiological Laboratory*, gives an admirable summary of the various ways in which nerve sections and nerve irritations may produce glycosuria. After showing that division of the fibres passing from the vasomotor centre in the medulla oblongata down the cervical part of the spinal cord, and thence along the vertebral arteries to the last cervical ganglion is followed by diabetes, he states that it is of great importance to notice that section of the sympathetic cord or splanchnic nerves does not produce diabetes, although the vasomotor nerves of the liver are thus divided. To quote Dr. Brunton textually: "The reason of this probably is that the vasomotor nerves of the intestine being divided at the same time, so much blood goes to the intestinal vessels that the circulation in the liver is not increased."

If this plausible explanation be admitted, it seems to me reasonable to argue that an undue contraction of arteries in other parts of the body than the liver may determine an excessive blood-pressure in the arteries of that organ, and so set up glycosuria, the liver itself not being necessarily at fault. There is one form of glycosuria to which I shall presently draw your attention as being possibly explained by such conditions.

The first practical point to which I should like to draw your attention is the influence of heredity in bringing about glycosuria. Of this my notes afford several instances. In one case both parents have passed sugar in the urine for many years; the father

dying at the age of 75, the mother being still alive at an age over 80. Here the eldest son, a remarkably powerfully-built and stout man of 55, has glycosuria. In another case the eldest daughter of a gentleman, who died also at the age of 75, after passing sugar for many years, has glycosuria to an amount justifying the application of the term diabetes. She is a tall very stout lady, enjoying apparently very good health; but she passes daily from 100 to 150 ounces of urine loaded with sugar. Again, a gentleman of extremely nervous temperament comes with intermittent glycosuria. His nervousness goes often so far as to annul self-control, so that he dare not travel about the streets of London without a companion; and his glycosuria appears mainly to coincide, in its development, with his perturbations. He states that his mother has diabetes, and is under restraint on account of mental aberration. My notes give me also two other cases of inheritance of a similar kind. They further present more than one case in which brothers, or brothers and sisters, of one family have had glycosuria. In one of these it is probable that one of the parents had been a subject of the malady. It is of course evident that the existence of glycosuria in minor degrees will have been often overlooked in the past, and that a better estimation of the transmission of the tendency will, in the future, be more possible under the steady maintenance of careful examination of the urine. I think it is certain that in many cases the disease is transmitted from parent to child; and it is worth our while to consider in what way the transmission may be ordered.

In the first case to which I have drawn attention there was a transmission from the father's side of gout as well as of glycosuria. Glycosuria is well recognised as a not infrequent symptom of gout; and here it is to my mind very probable that the gouty diathesis determined in each case the occurrence of the glycosuria.

Glycosuria, again, is certainly often observed in people subjected to great nervous strain, and in victims of excessive nervous irritability. Here, again, the possibility of a double transmission must be before us. But, when we come to consider cases in which these conditions are absent, a different view is presented.

Gout and nervous disorder being absent, both in parent and child, it is reasonable to suggest that tissue imperfection is to be invoked. In the second case which I have quoted the lady who presents a sharp glycosuria is also abnormally stout. Her father, it may be noted, had at one period of his life been of very full habit.

The conjunction suggests that her tissues are, in more than one way, abnormal tissues; that, correlated with the excess of fat, there may be an imperfect constitution of glycogen, rendering it unstable and prone to change. In considering heredity observed in diabetes we surely have not only to recognise the handing down of morbid processes, but also the handing down of various constitutions and modes of behaviour of the several tissues.

The occurrence of glycosuria in very stout people is certainly a noteworthy fact. I have seen it in people stout by inheritance and without other sign of disease; in people stout by reason of unwise habits of life, sometimes in the way of want of exercise, notably in the way of alcoholic indulgence; and I am inclined to regard both the accumulation of fat and the occurrence of glycosuria as marks of imperfect forms of nutrition. In addition to these causes we cannot overlook the influence of persistent alcoholic excitement of the liver in many cases included in the group just referred to. I find in my notes records of many cases in which, together with obesity, there were marked indications of affection of the liver. In most cases the liver was enlarged and tender; in a much smaller number, reduced. In most, with the alteration in the size of the liver, there coincided such symptoms as occasional jaundice, morning sickness, and great impairment of appetite. It is fair to suppose that in such cases the irritation of the liver by alcohol produced a reflex active hyperæmia, and consequently glycosuria, so that the relation of corpulence to glycosuria is decidedly complex. It is necessary, however, to remember that not a few of the victims of alcoholism come to us emaciated and still present glycosuria. I am much interested in finding that, in a very considerable proportion of cases of this class, valvular disease of the heart is detected, in addition to the affection of the liver. At first sight this, by causing backward pressure into the liver, would appear to oppose the introduction into that organ of an excessive amount of arterial blood. I am not prepared at the present moment to explain the part taken, if any, by the valvular disease in the favouring of glycosuria. But the concurrence comes out strongly in my records and must

demand further attention. I think it probable that irregularities of arterial tension will here have to be considered.

There is another group of cases which I think must be placed in close approximation with the foregoing. We not infrequently find that people presenting in a typical form the symptoms of contracting granular kidney have also glycosuria. Within the last few weeks I have seen a farmer, aged 60, who presented all the symptoms of contracting granular kidney of about a year's duration. He had no valvular disease; had a considerable enlargement of the liver, and, it is to be noted, much anasarca. His urine was of specific gravity 1022, contained a good deal of albumen, and gave a very definite sugar reaction. He had been a stout man, but was now much wasted, and had not been guilty of alcoholic excesses. He had no definite sign of gout. Now, whether in this case the glycosuria was due to a general defect of assimilative or constructive process, or related with a very definite arterial tension, is not easily to be decided. I put it forward as one of the many problems awaiting solution in the study of glycosuria. To these I will at the moment add another. I have observed the occurrence of glycosuria in two cases of Raynaud's disease, and with these I may couple the notes of a case which I had the opportunity of watching for several years. The patient was a gentleman of the age, when I first saw him, of 64. He was rather stout, had albuminuria and casts in the urine, and was passing a good deal of sugar without polyuria.

When I found these conditions I put him upon a careful diet, which, I am bound to say, he entirely disregarded. Shortly afterwards circular sloughs of very slight depth made their appearance on his legs, about equally on both. Their form made me suspect the influence of syphilis, but upon this point he was not communicative. The history of his children makes it pretty certain, however, that he had had syphilis severely. I treated him with iodide of potassium and kept him at rest for many weeks, with the result that the sloughs separated and the wounds healed. He now remained fairly well, though with diminished faculties, for six years, and then again consulted me for the reappearance of sloughs, now mainly confined to his left leg, in which I found, in addition to extensive sloughs still of a superficial character, a complete obstruction of the femoral artery, which certainly had not existed before. Placed in bed and carefully nursed, while the administration of iodide of potassium was steadily maintained, he survived for more than six months. Renal disease, glycosuria, and syphilis seemed all to have played their part in the fatal termination, and to the end there was no such general sloughing as one would have expected to result, in such a damaged constitution, from the blocking of the femoral artery. Here is another illustration of the complexity of the symptoms which are found in many cases of glycosuria, or I may perhaps say of the complexity of the causes which may determine the occurrence of glycosuria.

I am here reminded of a case which I recorded many years ago, looking at it from a different standpoint from the present. A young man of 25, who had contracted syphilis, consulted me on account of mischief in the mastoid process. The mischief turned out to be of a very serious character. On examination of his urine I found that it contained both albumen and sugar in considerable quantities. The albumen was pretty clearly referred to contracting granular kidney, but the sugar was not so easily disposed of. The first idea in any way of explanation was that irritation had spread from the mastoid process, inward to the medulla, and had affected the glycosuric centre therein. The next idea was that the liver might be involved in the meshes of syphilis, and be consequently disordered in its glycogenic function.

I must confess that the case at the time engaged my attention chiefly in respect of the remarkable form of uric acid observed in the urine, which indeed led me to undertake a prolonged observation on the influence of the constituents of urine normal and abnormal upon the form of uric acid as observed under the microscope. Whatever may have been the cause of the glycosuria in the case to which I refer, it is evident from cases which I have since seen that glycosuria is often present in cases of tertiary syphilis, and under conditions not involving irritation of the medulla.

My notes supply me with several instances of the association of glycosuria with tertiary syphilis without the least suggestion of implication of the medulla. The well-known incidence upon the liver of the effects of tertiary syphilis leads me to presume that hepatic irritation is mainly chargeable with the production of the symptom of glycosuria; and on review of my subsequent cases I

find that signs of hepatic disorder were always present. But I dare not speak in any tone of decision upon this point, being confronted by the profound alterations in general nutrition brought about by syphilis, and by the recognition of the possibility that, independent of hepatic irritation, faulty tissue-building may have to be considered: and such defect of anabolism may not concern the liver only. We know that there are other organs in which glycogen is formed and stored, notably the muscles. And as I review glycosuria as it has presented itself to me, I experience much doubt as to whether I have not been keeping the liver too pre-eminently in my mind. The comparatively small amount of sugar found in the urine of many persons fairly advanced in life may possibly be inadequate to the majesty of that great organ. I know of no methods of analysis which may enable us to distinguish a glycosuria of hepatic origin from one of muscular origin. I can see no reason which should prevent a glycosuria from being the result of perturbations in the several glycogen-forming structures respectively; that is to say, it seems to me quite possible that a disturbance of nutrition in muscles, in spinal cord, and in liver might exist independently in each and give rise to glycosuria, while, on the other hand, a deep dystrophy might affect all at once. You will see that the consideration is rather wide, and I think that it offers a problem worthy of careful analysis.

I will pass now to another somewhat new aspect of glycosuria. In the paper to which I have already referred I noted several cases in which glycosuria or, as it has been called, diabetes, preceded, or was preceded by, angina pectoris, and subsequently co-existed with it. Several cases of the same kind have since come under my knowledge. I will venture to detail one which was under my observation for some time.

A gentleman, of the age of 62, consulted me in June, 1886, complaining, in the first place, of a cough which had been distressing him for six weeks. The cough did not appear to be due to any affection of the lungs, heart, or stomach, but rather was attributable to a deep dusky congestion of the throat, such as one often sees in gouty people. The patient was a man of singular refinement and delicacy, and at the same time of much acute sensitiveness and irritability. He had lost flesh, complained of low spirits, of much unfounded anxieties, and of serious want of sleep. His urine was at that time of specific gravity 1020, and while containing no albumen, gave a very decided reaction of sugar. I prescribed for him a careful diet, bromide of ammonium and codeia, but did not see him again till some weeks later, when he was the subject of a very sharp attack of quinsy—a typical gouty quinsy. During this attack the sugar disappeared entirely from the urine, but albumen made its appearance. After the attack the sugar returned, but in smaller quantity, and for a time his health improved; but in June, 1887, after an absence of several months, he came to me with new symptoms. They were, in the first place, symptoms of angina pectoris. He lived in a suburb from which a train took him to the city. To catch the train it was necessary that he should walk up a short acclivity beginning at his garden gate. Starting from home, shortly after breakfast, he was obliged, after walking a few yards, to stop and hold on by the palings, feeling, as he said, as if he were ready to die by reason of a strong sense of constriction of the chest, which seemed to be about to stop him altogether from breathing. After holding on for a few minutes he would recover his breath, and would generally be able to walk to the station. Sometimes, however, a second attack would intervene. At this time, although he had gained flesh, his general condition was a good deal worse than it had been a year before. His heart was now decidedly enlarged, and the enlargement appeared to be due chiefly to dilatation on both sides. The heart sounds were weak and obscure, and although I could detect no definite murmur I came to the conclusion that there was not only impaired nutrition of the muscular wall, but commencing valve disease. He was still suffering from much irritability and insomnia. The urine was now of specific gravity 1028, contained a little albumen, and gave a strong reaction of sugar. Rest, diet, and the use of strophanthus, in addition to codeia, brought about some improvement for a time. But three months later I was called, in great haste, to see him in consultation with his usual medical adviser. I found now that he had constantly recurring attacks of angina, by day and by night, altogether independent of muscular exertion. A careful examination led to the establishment of the diagnosis of sharp gastric catarrh. He had a foul tongue, thirst, frontal headache, nausea, occasional vomiting, and loss of appetite. The urine contained still a little albumen and much sugar. I advised careful evacuation of the bowels

and the use of sedatives for the stomach in the form of carbonate of bismuth, with bicarbonate of potash and tincture of belladonna. But before these remedies could have time to operate, his sufferings increased to a terrible degree. His attacks of angina were almost continuous, and he had to sit night and day with his head supported on a rest in front of him. Under these circumstances, many remedies were used by those in immediate charge of him. Nitro-glycerine and nitrite of amyl were of some use. For the insomnia various hypnotic remedies were applied. But it appeared to me that they were only of temporary value, and that the essential method of treatment was to overcome the gastric catarrh. It seemed that this definitely established condition was the abiding cause of the angina, so we resolutely attacked it with various remedies until it yielded. When it passed away, the angina gradually diminished, and the patient was able to leave his house and go to Margate, where he remained for some time in comparative comfort—until one day, moving suddenly from the breakfast table, he was seized with a fatal attack of angina. During all this illness, his urine was carefully examined. There were, indeed, difficulties in the way of estimating the quantity of urine passed daily; but the quantity of sugar in the specimens examined was always greater than it had been before.

I could cite other cases, but will only say that the same kind of association has been more than once observed. Now, if we carefully consider what is called angina pectoris, I think we must admit that it is no more an essential disease than glycosuria; and, as I have seen it, and thought over it, I recognise in its varieties of form and causation which run in curiously parallel lines with those of glycosuria. Every one, no doubt, must recognise the typical form of angina pectoris wherein degeneration of the heart muscle plays one part and arterial stress another; and everybody also will, I think, be ready to admit that disorder of innervation plays an important part in disturbing the balance between the heart and the arteries. Not improbably, indeed, this may be the first and common factor. In such a case as I have just described it looks very much as though disordered innervation was the starting point of the whole mischief.

If it were so, the position of the glycosuria has to be fixed. It might have been also a mark of disordered innervation. It certainly preceded heart and stomach disorder; and after being a herald of them, increased as they began and developed. But if the glycosuria were of hepatic origin, it seems to be necessary to admit that while there was undoubted tension of peripheral arteries in the limbs and head and neck, there must have been dilatation of the hepatic artery, or indeed some defect of digestion or of assimilation. It is impossible to eliminate entirely the last two causes, or to estimate their possible value. But comparing this with other cases, I cannot help cogitating in what ways disturbance of the arterial circulation of the liver may possibly occur in angina.

It is I think quite certain that excitements of the central nervous system may produce at one and the same time arterial relaxation in one part of the body and arterial contraction in another. One often sees people who, under one or the other form of perturbing influence, become flushed and hot in the face and cold in the extremities, or hot in the extremities and cold in the face.

In such a case as that which I have quoted we might, on the one hand, recognise a perturbing nervous influence as a cause of peripheral arterial tension, of defective nutrition of the heart, of glycosuria, and probably of the faucial and gastric affection.

There is much reason in fact to look upon this as the best explanation of the whole array of phenomena. But in a preponderance of the cases presenting glycosuria together with symptoms of angina, the evidence of primary neurotic disturbance has not been so strong. In thinking over these I have been inclined to recur to a point shortly dealt with in the commencement of this paper, and to consider how far it might be possible that excessive tension of the arteries in one part of the body might be, so to speak, balanced by excessive blood pressure in arteries or other parts of the body. Surely this is what we, in a way, invoke when we attribute an internal inflammation to a chill of the external surface, or when we apply an irritant to the surface of the body in order to reduce inflammation in an internal organ. In addition we must not forget the reflex influence of one organ on another. Stomach disorder may have had its share in the production of the glycosuria, as it certainly had, in the case quoted, its share in the intensification of the angina. As one studies angina, one certainly finds that many apparently access-

sory conditions have to be dealt with in its treatment, notably for one, constipation.

All constipation is certainly attended with increase of arterial tension. In the treatment of angina I have found practically that the maintenance of a daily action of the bowels has been a need of the first importance, just as I have found that the avoidance of over-filling of the stomach, often resorted to where the patient is weak and failing, is imperatively necessary.

But I must not be diverted into a paper on angina, and I do not at the present propose to enter further into the relation of affections of the nervous system with glycosuria than has been dealt with in my former paper, and illustrated in this.

I have but one conjunction to put before you. A year or two ago one of my house-physicians, Mr. W. W. Ord, making thorough examination, according to rule, of a patient just admitted to St. Thomas's Hospital, found that her urine gave a strong reaction of sugar. She had been admitted for acute rheumatism, arising during lactation. Her child having been separated from her, it had been necessary to use applications to stop the flow of milk. The breasts had been strapped with belladonna plasters, and extract of belladonna had been applied over the nipple areolæ. The examination of the urine was made within a few hours after the institution of this treatment, which evidently proved effective in staying the secretion of milk. After the detection of sugar, frequent examination of the urine was made. The sugar reaction turned out to be most marked in the beginning, and gradually diminished until at the end of three days it had entirely disappeared. Similar observations have been made in six cases—four in St. Thomas's Hospital, two at the Cane Hill Asylum. The chemical reactions obtained have appeared to correspond exactly with those which would be yielded by glucose, but their rapid evanescence has so far stood in the way of the obtaining any sufficient quantity of urine to afford opportunity of a complete investigation. The indication is, apparently, that the stoppage of the secretion of milk has determined a backward flow into the vessels of lactose in a quantity so large as to be represented by the appearance of a considerable quantity of glucose in the urine. That lactose introduced into the system as a constituent of milk through the stomach, not only acts as a diuretic, but gives rise to glycosuria is asserted by M. Germain Sée. About last mid-summer my friend Dr. Keser was good enough to send me a copy of the *Semaine Médicale* of June 12th, containing a note on "Un Nouveau Médicament Diurétique dans les Maladies du Cœur, la Lactose."

I have since seen many references to this paper, which states that an enormous diuretic action is established by the use of 100 grammes of lactose (that is to say, the quantity contained in two litres of milk), while there is no certainty of obtaining this effect by four or five litres of milk. M. Sée goes on to say that while milk taken in large doses produces diuresis and a very marked glycosuria, large doses of lactose cause a remarkable polyuria, but no glycosuria. My house-physician's observation would appear to agree with this, so far as the suppression of lactation is concerned. The two sets of notes appear to confirm one another.

Both appear to me to suggest questions that should be carefully worked out. Why lactose given by itself should produce diuresis without glycosuria; why lactose given with other constituents of milk should give rise to both, while requiring a larger dose, is what at present I do not profess to understand.

M. Germain Sée believes that the sugar remains in the blood when lactose is administered pure. With all respect to him, I think that the whole conditions require further elucidation.

With this I conclude my paper this evening. I trust that you will understand that I have been, so to speak, talking from my notes, thinking of the many ways in which glycosuria presents itself as a symptom in various diseases and disorders, and trying to find out what may be the instruction afforded in the several instances of sugar in the urine.

On the subject of treatment I do not propose to dwell to-night. If my views of the analysis of the causes of glycosuria are at all to be admitted, it must follow that the treatment of a subordinate glycosuria must be involved in the treatment of the major part of the case.

Not many years ago, when albumen was found in a patient's urine he was supposed to have Bright's disease. So now it is very often the practice to speak of the existence of a small quantity of sugar in the urine as justifying the use of the term diabetes. I think that those who have studied the question most thoroughly will agree with me that this is a most unwise use of

the term; unwise as bearing alike upon prognosis and treatment. Finally, I trust you will see that all I have put forward is rather analytical and suggestive than final or didactic. I wish to submit for your criticism, and to propose for your investigation, certain associations of glycosuria which have presented themselves to me, and to which I have devoted a good deal of thought.

A DISCUSSION ON RECENTLY INTRODUCED HYPNOTICS AND ANALGESICS.

*In the Section of Pharmacology and Therapeutics at the
Annual Meeting of the British Medical Association, held in
Leeds, August, 1889.*

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THE medical profession is often reproached with the slowness of the advance of therapeutics, and certainly, with regard to many classes of remedies, we cannot boast that we know much more than those who have preceded us in the practice of medicine, but, in some directions, especially where the chemist, the pharmacologist, and the practical therapist have been able to work together, there has been progress, and many new and potent remedial agents have been introduced.

As a result of such combined work the hypnotics, and analgesics especially, have been largely added to, but the comparative utility of the new agents is by no means definitively settled. An interchange of experiences of many observers, extending over a wide area of the field of disease, is essential for determining the exact value of any new remedy, and for such interchange this Section is especially adapted.

I propose to limit my remarks, for the most part, to the hypnotics connected with the fatty series. In this class, however, are contained all but three of the newer sleep-producing agents, and of these two, hyoscyne and tannate of cannabin, are only old friends with new faces, whilst the third, boldin or boldo-glucin, has neither been thoroughly investigated nor practically employed.

The following is the list of hypnotics connected with the fatty series which have been brought into use in the past seven years:—

1. Urethane $\begin{array}{l} \diagup \text{NH}_2 \\ \text{C} = \text{O} \\ \diagdown \text{OC}_2\text{H}_5 \end{array}$
2. Acetal (diethyl-acetal or ethidine-diethyl-ether) $\begin{array}{l} \diagup \text{OC}_2\text{H}_5 \\ \text{CH}_3\text{CH} \\ \diagdown \text{OC}_2\text{H}_5 \end{array}$
3. Methylal (methylene-dimethyl-ether) $\begin{array}{l} \diagup \text{OC}_2\text{H}_5 \\ \text{CH}_2 \\ \diagdown \text{OC}_2\text{H}_5 \end{array}$
4. Sulphonal (diethyl-sulphon-dimethyl-methan) $\begin{array}{l} \text{C}_2\text{H}_5\text{SO}_2 \diagdown \diagup \text{CH}_3 \\ \text{C} \\ \text{C}_2\text{H}_5\text{SO}_2 \diagup \diagdown \text{CH}_3 \end{array}$
5. Amylene hydrate (dimethyl-ethyl-carbinol or tertiary amyl-alcohol) $\begin{array}{l} \text{C}_2\text{H}_5 \diagdown \\ \text{C} \text{---} \text{H} \\ \text{C}_2\text{H}_5 \diagup \end{array}$
6. Paraldehyde $(\text{CH}_3\text{COH})_3$
7. Hypnone (aceto-phenone or methyl-phenyl-ketone) $\begin{array}{l} \text{C}_6\text{H}_5 \diagdown \\ \text{C} \text{---} \text{H} \\ \diagup \text{CO} \end{array}$
8. Chloralurethane $\begin{array}{l} \diagup \text{OH} \\ \text{C Cl}_3 \text{---} \text{C} \text{---} \text{H} \\ \diagdown \text{NH COOC}_2\text{H}_5 \end{array}$
9. Chloralamide $\begin{array}{l} \diagup \text{OH} \\ \text{C Cl}_2 \text{---} \text{CH} \\ \diagdown \text{NHC OH} \end{array}$

The fact that hypnotics have been sought for and so largely found amongst combinations connected with the fatty series is well worthy of note.

In the admirable Croonian lectures delivered by Dr. Lauder Brunton¹ before the College of Physicians—lectures which must be looked upon as marking an epoch in scientific therapeutics, and serving as a point of departure for future investigations, the dependence of physiological action on chemical composition, in the case of hypnotics as well as of other groups of remedies, has been ably pointed out. I will not deal at length with this part of the subject; nevertheless, it is desirable that I should refer briefly to it before pointing out the nature of the substances I am about to speak of.

The alcoholic radicles or alkyls, that is, the substances belonging to the series $\text{C}_n\text{H}_{2n+1}$, of which methyl (CH_3) and ethyl (C_2H_5) are familiar examples, tend to give the compounds into which they enter a power of depressing the functions of the higher cerebral centres and of producing either sleep or that complete insensibility to external impressions known as general anaesthesia; by their further action the motor and reflex centres are weakened, and eventually the vasomotor and respiratory centres and the cardiac ganglia lose their power, the nervous centres being affected in the inverse order of their development.

In some combinations the influence of the alkyl element is not apparent, as, for example, in methyl hydride CH_3H , and acetic acid (CH_3COOH). If, however, the molecule of H, or of COOH , be replaced by OH or COH we get methylic alcohol (CH_3OH) and aldehyde (CH_3COH), in both of which the influence of the alkyl element on the nervous centres is manifest.

Very little is known as to the laws which govern the appearance of this influence in the various classes of combinations into which the alcoholic radicles enter, but it is possessed by so many of these combinations that pharmacologists have been led to search amongst them for those which most effectively depress the higher nervous centres without exerting a deleterious influence in other ways, and this search has led to the large addition to our sleep-producing agents shown in the list.

The halogen elements, chlorine, bromine, and iodine, have, too, a tendency to depress the functions of the higher nervous centres, but they likewise tend more than the alkyls to depress the functions of those lower centres which preside over respiration and circulation, and they influence the heart more markedly, weakening its action; the combination of an alkyl with chlorine, or the replacement of one or more of the molecules of hydrogen in an alkyl compound by chlorine, will in many cases augment its influence on the nervous system; but at the same time it increases its depressing effects on the circulation and respiration. It is on this account that chloral hydral ($\text{CCl}_3\text{CH}(\text{OH})_2$), though an admirable hypnotic, may give rise to evils which are not produced by the newer and non-chlorinated hypnotics. By combining chloral with other groups, it has been sought in some degree to minimise these possible evils, and the two last substances in the list have been introduced with this view.

Apart from chemical structure, the physical properties of compounds influence their physiological effects; hence it is that some of the combinations into which alcoholic radicles enter are anaesthetic, some hypnotic; anaesthetics being found amongst those substances which are volatile and quickly eliminated, soporifics amongst those which have a heavy molecule and are either liquid or soluble in form, so that they may be given by the mouth, and, being absorbed into the blood, may continue to act.²

As the action and utility of hypnotic agents are greatly affected by their physical characteristics, I will shortly set forth the points of chief importance relating to them.

Urethane is a solid, very soluble in water, without much taste, and without unpleasant smell, though some specimens have a foul, mouselike odour, due probably to acetamide, produced during the manufacture of the drug.³ It was introduced by Schmiedeberg in 1885.⁴

Acetal is a light-coloured fluid with an unpleasant smell and taste, which was proved by von Mering⁵ to have soporific properties in doses of one to three drachms.

Methylal is a motile, colourless fluid, with a chloroform-like smell and pungent, slightly bitter taste. When impure, as Dr.

¹ JOURNAL, June, 1889.

² Brunton, JOURNAL, June 29th, 1889.

³ Med. Chron., September, 1888.

⁴ Practitioner, vol. xxxv.

⁵ Berl. klin. Woch., 1882, vol. ii, p. 43.