TABLE OF URIC AND PHOSPHORIC ACID EXCRETION—Continued.

Case No.	Total Quantity Urine in 24 hours.		Ratio of Uric Acid to Phosphoric Acid, the former being assum'd as 1	
	Uric Acid.	Phos. Acid.	Uric Acid.	Phos. Acid.
NEURASTHENIA—Continued.				
110.	.326	.496	1	1.52
111.	1.996	6.105	1	3.05
112.	.56	2.1	1	4.03
113.	.435	1.45	1	3.33
114.	.418	1.28	1	3.06
115.	.144	.75	1	5.2
Av.	6.11	1.612	1	2.6
NEURITIS.				
115.	.664	1.	1	1.5
OBESITY.				
116.	2.06	2.89	1	1.4
PARALYSIS.				
117.	.3	.36	1	1.19
118.	.786	1.62	1	2.06
119.	.95	1.52	1	1.6
Av.	.678	1.16	1	1.71
Case No.	Total Quantity Urine in 24 hours.		Ratio of Uric Acid to Phosphoric Acid, the former being assum'd as 1	
	Uric Acid.	Phos. Acid.	Uric Acid.	Phos. Acid.
PYELITIS.				
120.	1.28	2.52	1	1.97
	1.38	2.52	1	1.82
	.8	2.4	1	3.
	.7	2.7	1	3.85
	.99	1.01	1	1.02
Av.	1.03	2.23	1	2.16
RENAL COLIC.				
121.	.757	2.15	1	2.84
122.	.73	2.85	1	3.82
Av.	.743	2.5	1	3.3
SEPTICEMIA.				
123.	1.77	.715	1	.42
Case No.	Total Quantity Urine in 24 hours.		Ratio of Uric Acid to Phosphoric Acid, the former being assum'd as 1	
	Uric Acid.	Phos. Acid.	Uric Acid.	Phos. Acid.
SPLANCHNOPTOSIS.				
124.	.66	.64	1	.97
SPLENIC ANEMIA.				
125.	.854	.84	1	.98
	1.57	2.83	1	1.8
Av.	1.21	1.83	1	1.5
TUBERCULOSIS (PULMONARY).				
126.	.54	3.72	1	6.81
127.	2.16	2.47	1	1.14
128.	1.45	.41	1	.28
129.	1.165	2.295	1	1.97
Av.	1.328	2.223	1	1.67
Gen'l				
Av.	.91	1.98	1	2.1

the uric acid, so that we have an extreme range of the ratio from 1 to .28 up to 1 to 16.1, the former ratio occurring in the case of pulmonary tuberculosis with 1.45 gm. of uric acid and .41 gm. of phosphoric acid, the latter in a case of angina pectoris, in which there was .26 gm. of uric acid and 4.2 gm. of phosphoric acid.

Perhaps the most striking feature of the entire series of analyses is the utterly *bizarre* tendency constantly shown in the absolute and relative amounts excreted. Yet the final average comes well within the range of the accepted standards. One surprising and possibly suggestive fact is the very large amount of uric acid excreted in Bright's disease, the average being something over 1 gm., while the average quantity of phosphoric acid was less than 2 gm. The large quantity of purin bodies, of which the uric acid may be taken as an imperfect index, is in line with the views already expressed concerning the toxic character of many of these bodies and the present conception of some sort of primary intoxication as the most probable initial phenomenon of that disease.

Another thing requiring explanation is the uric acid output in diabetes. It is pretty uniformly agreed that the results obtained by the Hopkins method in diabetes are unreliable and that some constituent of the urine in diabetic patients gives the reactions of uric acid, which, instead of being very high, is really less or only slightly greater than the average. It probably would have been as well to have omitted them, but they are allowed to stand with this explanation for whatever they are worth, as the cases had all been numbered and tabulated and the computations made before the question was reached. I have not gone over the literature of this question and so do not know the ground of this conclusion, which seems to be uniform, but I am at a loss to understand why uric acid should be below the normal in a disease attended with a tremendous urea output, perhaps the largest of any disease, and in which the morbid activity of metabolic processes would be expected to produce rapid nuclein disintegration with the production of large quantities of purin bodies.

It may seem a little curious at first sight that a clinical study of the uric and phosphoric acid excretion in so considerable a number of cases should not include

a single case designated as gout. It is in part accidental, as I did not ask for selection of any particular group or groups of cases, and in fact it is due to the fact that gout was usually a subordinate diagnosis in my case records. At any rate, it appears to me to be unimportant, as I am fully convinced that uric acid is only an incident in gout and that neither its formation nor excretion is in any sense a key to the disease.

DISCUSSION.

PROF. GRAHAM LUSK, New York City, said it seemed to him that the purin base elimination has not been sufficiently investigated. It has been found by Dr. A. R. Mandel that the temperature in fever follows parallel with the elimination of these bases. This matter is being more fully investigated by Dr. Mandel.

LACTIC ACID IN METABOLISM.

WITH A NOTE ON THE CAUSE OF FATTY CHANGES IN THE ORGANISM.*

ARTHUR R. MANDEL, M.D.

AND

GRAHAM LUSK, Ph.D.

NEW YORK CITY.

The first researches on the subject of metabolism sought to determine the quantity of proteid, fat and carbohydrate destroyed by an organism in a given time and under definite conditions. Much has recently been accomplished toward an explanation of the intermediary steps involved in the destruction of the foodstuffs by the organism. Thus glycocoll, a product of proteid metabolism, may be united with benzoic acid in the organism and be eliminated in large quantity in the urine, but no similar method will cause the elimination of leucin, or of alanin, products of proteid destruction.

The present research concerns the subject of the position of lactic acid in general metabolism, and represents work accomplished at various times during two and a half years, involving feeding experiments on 24 dogs.

* Read in the Section on Pathology and Physiology of the American Medical Association, at the Fifty-seventh Annual Session, June, 1906.

* From the Physiological Laboratory of the University and Bellevue Hospital Medical College.

Hoppe-Seyler believed that when dextrose was destroyed in the body it first broke up into two molecules of lactic acid. Neucki and Sieber¹ gave a diabetic patient 20 gms. of sodium lactate and found none of it in the urine. They concluded that the lactic acid was completely burned and that if the diabetic could acquire the power to split dextrose into lactic acid the further metabolism of the latter would be assured. They overlooked the fact of a small but definite rise in the output of dextrose in their diabetic patient, which to-day would be explained by assuming a synthesis of dextrose from the lactic acid ingested.

Embden and Salomon have endeavored to prove that dextrose may be synthesized from ingested lactic acid, by giving diabetic dogs sodium lactate. The dogs were depancreatized, but apparently not completely. In one case there was no sugar in the urine until after the administration of the lactate, and in another experiment the sugar output rose 10 gms. after administering large quantities of the lactate. These results are open to the criticism that the ingestion of sodium ions may increase the permeability of the kidney epithelium for dextrose (Fisher, Muderhill and Closson).

Some time before the publication of Embden's experiments mentioned above, we ourselves had given sodium lactate to a dog diabetic with phlorizin, and had found that 70 per cent. of the l-lactic acid given was convertible into dextrose, while the rest burned and reduced the proteid metabolism. In phlorizin diabetes there is little difficulty in establishing a definite ratio between nitrogen and sugar in the urine, which in fasting dogs approximates 3.65 gms. of dextrose to 1 gm. of nitrogen. Any dextrose present in excess of this ratio is "extra sugar" which must have some source other than proteid. In experiments with lactic acid ingestion, the "extra sugar" would represent the amount of sugar produced from lactic acid given.

The conversion of 70 per cent. of lactic acid into dextrose with a reduction in the proteid metabolism recalls the behavior of cane sugar in pancreas diabetes. Minkowski showed that the dextrose component was completely eliminated in the urine, while the levulose molecule was in part converted into dextrose and eliminated and in part burned, and reduced the proteid metabolism of the period.

We wished to find if a similar analogy existed for lactic acid, and therefore procured some d-lactic acid from Kahlbaum. This substance was not perfectly pure, but its subcutaneous ingestion in the form of a sodium salt resulted in one instance in its complete elimination as "extra sugar" in the urine of a diabetic dog. Its administration never resulted in a reduction in the amount of proteid destroyed. It appears, therefore, that d-lactic acid given to a phlorizinized dog may be completely converted into dextrose, while l-lactic acid may be in part so converted, and may in part burn within the organism. Just as dextrose is the sugar of the blood, so d-lactic acid is the acid found. The latter is present in all normal tissues and in increased quantities in arsenical and phosphorus poisoning.

The next question which arises is the possible production of lactic acid from dextrose in metabolism. Stoklasce has isolated a ferment from animal tissues which converts dextrose into lactic acid. The strict proof of this conversion is afforded by the experiments of Embden, who found that the percolation by blood of a liver

rich in glycogen resulted in the accumulation of lactic acid in the blood. Also the percolation of a liver free from glycogen by a blood rich in sugar caused the formation of lactic acid, whereas the use of a blood poor in sugar had no such effect.

Claude Bernard saw that dextrose was convertible into glycogen and this again back into dextrose. It is evident that d-lactic acid may now be added to both ends of this chain forming the sequence: lactic acid, dextrose, glycogen, dextrose, lactic acid.

This is not the whole story, for lactic acid is known to be derived from proteid. Minkowski showed this when he extirpated the liver in birds and found ammonia and lactic acid replacing uric acid in the excreta, and in amounts proportional to the proteid metabolism. Also Asher and Jackson, after tying the arterial supply to the intestinal canal, spleen, pancreas, liver and kidney of a dog, noted an accumulation of lactic acid in the blood of the animal. The life of this dog was essentially carried on by the heart, which pumped blood through the muscles and lungs. Theoretically, lactic acid may arise from proteid through the hydrolysis of a substance like alanin, as is indicated in the following reaction:

von Noorden and Embden suggest the cleavage of leucin, a proteid decomposition product, into a radicle convertible into acetone and into alanin, which, as has been shown, is convertible into lactic acid. This cleavage of leucin is illustrated as follows:

If alanin is convertible into lactic acid in the organism, it should also be convertible into sugar and, indeed, Neuberg and Langstein find that its ingestion increases the quantity of glycogen in the liver, and Amalagia and Embden show that it may bring about a large increase in the quantity of dextrose eliminated by a diabetic dog.

In phosphorus poisoning lactic acid accumulates in the tissues and blood of a fasting dog and appears in the urine. The urine is ammoniacal. Ray, McDermott and Lusk found on administration of phlorizin to such a dog that there was an elimination of dextrose in the urine which was in no way different from that excreted in uncomplicated phlorizin diabetes, and that the ammoniacal reaction disappeared. We have repeated these experiments and have analyzed the blood and urine for lactic acid as well as for nitrogen and dextrose.

It has been found that while lactic acid was present in normal blood, and in the blood and urine of dogs poisoned with phosphorus, it disappeared in all cases from both blood and urine when phlorizin diabetes was induced. Phosphorus poisoning will not cause lactic acid accumulation when dextrose is completely removed from the body, as in the case of phlorizin diabetes.

How is this to be explained? It seems to us that in phosphorus poisoning the lactic acid produced from proteid is synthesized in the organism (liver) into dextrose, and this dextrose when transported to the tissues is only partly burned, part of it reaching the lactic acid stage only, which lactic acid may return to the blood to be perhaps again reconverted into dextrose. It seems probable that phosphorus acts directly or indirectly to reduce the activity of the enzyme which normally breaks up the lactic acid derived from dextrose metabolism in the tissues.

1. Neucki and Sieber: Jour. f. prak. Chemie, 1882, vol. xxvi, p. 41.

It has recently been stated by a number of German writers (Jacoby, Waldvogel, Oswald) that phosphorus induces autolysis of the body's protoplasm. This is not true. If one administers phosphorus to a fasting dog, the proteid metabolism may be increased to 250 per cent. of that observed in starvation. If phlorizin diabetes be induced in a fasting dog this rise may extend to 500 per cent. This latter increase is due to the non-combustion of the carbohydrate derived from proteid. If now a phlorizinized dog be given phosphorus there may be absolutely no further rise in the nitrogen elimination in the urine. The mere administration of phosphorus, therefore, can not cause an uncontrolled activity of proteolytic enzymes in the organism. It is much easier to explain the rise in proteid metabolism in phosphorus poisoning as due to an incomplete combustion of lactic acid.

Another analogy in these two cases is the fatty infiltration found in the tissues both in phosphorus poisoning and in diabetes. The cause is similar in both cases. In diabetes, when the sugar does not burn in the cells, the "sugar-hungry" cells attract fat in greater quantity than they can burn it. The blood may become full of fat which is being transported. In phosphorus poisoning, there is a modified "sugar hunger" in that lactic acid, a primary cleavage product of dextrose, does not burn—hence the fatty infiltration. Whenever such conditions exist, fatty infiltration occurs. It has been found by Hoppe-Seyler and Araki that a diminished oxygen supply to the body results in the appearance of lactic acid, and in all such cases fatty changes occur. A local diminution in the blood supply to a part of the heart, for example, will produce this condition with resultant fatty infiltration. In the lactic glands, where dextrose is probably converted into milk-sugar, which latter can not be burned in the organism, there are "sugar hungry" cells which attract fat from the blood. Even the fatty degeneration observed on autopsy in fever cases may be due only to dyspnea which precedes the fatal outcome. These views have been gradually developed in this laboratory, and are but an extension of Rosenfeld's discovery of a physiologic antagonism between glycogen and fat deposit in the liver.

CHRONIC CATARRHAL DEAFNESS.

NOTES ON SOME VERY SIMPLE EXPERIMENTS AS TO THE INFLUENCE OF SOUND WAVES ON OSSICULAR RIGIDITY.*

PHILIP D. KERRISON, M.D.

Clinical Lecturer on Diseases of the Ear, University-Bellevue Medical College; Aural Surgeon Willard-Parker Hospital; Assistant Aural Surgeon Manhattan Eye and Ear Hospital.

NEW YORK CITY.

That most cases of chronic catarrhal deafness are due largely to rigidity of the ossicles depending on morbid changes within the tympanum is an etiologic truism. The correction of this condition by some form of passive exercise—exercise that will move, not segments of the drum membrane, but the drum membrane and ossicles together—is not yet within our grasp. It is a fascinating possibility, a problem the solution of which would be of more value to humanity than could possibly result from the most brilliant development of otology along any other lines.

METHODS USUALLY EMPLOYED.

I wish (1) to consider, briefly, the methods usually employed for exercising the drum membrane and ossicles, and (2) to speak of some very simple experiments as to the influence of sound waves on ossicular rigidity. Of the various measures employed, inflation and pneumatic massage are in most common use.

Inflation of the tympanum either by catheter or the Politzer method is of the greatest value in cases of tubal catarrh or obstruction as a means of replacing the drum membrane in its normal position and re-establishing the function of the tube. Beyond this, its value as a means of correcting ossicular rigidity is distinctly limited. I assume that this proposition will be accepted without argument.

Pneumatic massage is a term applied to passive movements of the drum membrane by means of any instrument producing alternate condensation and rarefaction of the air in the external auditory meatus. I have employed this measure in a considerable number of cases, using either Siegel's otoscope or a pneumatic pump connected with the electric motor. With either instrument I have invariably kept the drum membrane under direct inspection and endeavored in this way to guard against the employment of too great force. In some cases a considerable immediate gain in hearing has resulted from a first application of this procedure. This gain has rarely proved permanent, however, and progressive improvement has never resulted from repeated use of this form of massage. On the other hand, distinct loss has seemed to follow its routine practice in a considerable number of cases.

The unsatisfactory results of pneumatic massage are probably explained by two facts: 1. The movements of the membrana tympani are not those which Nature requires of it or which are necessary to the transmission of sound waves, and do not, therefore, exercise the drum membrane and ossicles in their normal function. 2. The undue strain to which the drum membrane is subjected tends to produce alterations in tension, reducing still further the patient's hearing power.

Pneumatic massage by the method under discussion seems to be based on the theory that whatever will move the ossicles will improve the hearing. Its practice does not seem to be governed by any rules based on scientific investigations, the method of its application to different cases being largely a matter of guess work. Should this statement be objected to, it may easily be disproved by any one who will throw light on the following questions: By what established rules is the relation between the degree of deafness and the number of vibrations employed to be determined? Should the length of the piston stroke vary in different cases? If so, by what method other than guess work are such variations to be regulated in accordance with the varying degrees of deafness or ossicular fixation? Recognizing the obvious fact that any loss of tension in the drum membrane will necessitate the employment of greater force, i. e., a longer piston stroke, in order to produce a given movement in the ossicular chain, how are such variations in tension to be determined and allowed for? Employing sufficient force to move the ossicles, how is undue relaxation of the drum membrane to be guarded against? These questions would seem idle except in so far as they may show weak points in a method of treatment from which much has been expected and which is still advocated by many distinguished aurists.

* Read in the Section on Laryngology and Otology of the American Medical Association, at the Fifty-seventh Annual Session, June, 1906.