STUDIES IN PHLORIDZIN GLYCOSURIA.

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THE glycosuria that appears after the use of phloridzin raises many points that are of value in elucidating the subject of sugar formation. This drug produces a glycosuria which, as all agree, is due to increased production and not to diminished consumption of sugar within the organism, and has its source in the proteids of the body.

Further, phloridzin glycosuria upsets the idea of the exclusive or predominating activity of the liver in sugar formation, and has attracted the attention of physiologists to the part played by the kidneys in producing diabetes.

Phloridzin glycosuria has been produced after extirpation of the liver in geese (Thiel[1]), after ligature of the hepatic duct (Wolkow) and after fatty degeneration of the liver (v. Mering). Diabetes as a result of kidney disease was first asserted by C. Schmidt in 1850. Since then the co-existence of diabetes and albuminuria has been frequently brought forward. Armani and Farraro have described hyaline degeneration in the epithelium of Henle's sheath, and Ebstein has found necrosis in the epithelium of the convoluted tubules.

In a remarkable research Ehrlich described glycogenic degeneration of the epithelium of the tube of Henle, and Straus in the main confirmed the observation. Both regarded the degeneration as a secondary one.

v. Mering was the first to suggest the participation of the kidneys in the production of phloridzin glycosuria. Minkowsky advanced the explanation that phloridzin was decomposed in the kidneys, and that the phloretin thus liberated became again united to sugar in the organism,

[1] See bibliography at end of article.

the compound so formed being again broken up in the kidneys. Uschinsky also urges strongly that the kidneys participate actively in the production of diabetes, though in my opinion he goes too far when he suggests that they do so in all forms of that disease.

In order to solve more exactly the problem of the part played by the kidneys in the formation of glycosuria I undertook during the past year a series of experiments upon the action of phloridzin on dogs. In all cases the phloridzin was administered hypodermically and during all operations referred to in this paper ether was used as an anaesthetic. I began by giving the drug and repeating the operation of ligating the blood vessels of the kidneys. I estimated the sugar in the blood of the carotid artery before and after the operation, which was performed by means of the lumbar incision. The separation of the proteids of the blood was accomplished by a saturated solution of sodium sulphate. To 80 c.c. of a saturated solution of sodium sulphate was added directly from the blood-vessel about 20 grammes of blood. (The amount of blood was determined by weight.) A few drops of acetic acid were added, and the mixture was heated until all the proteids were coagulated. The mass was then filtered; the precipitate was washed with a hot saturated solution of sodium sulphate; and the washings and filtrate were tested for proteids and albumoses. They were usually absent. The sugar was then determined by the usual volumetric method with Fehling's solution.

My experiments have fallen naturally into four groups.

Group A.

This group comprises the experiments on the effect upon the sugar of the blood of ligation of the renal blood vessels after the administration of phloridzin.

Exp. I. Dog, 5·8 ks. in weight. Blood was taken from the carotid artery and the amount of sugar in it was found to be 0·120 %. 1·5 grs. of phloridzin were then injected. At 10 a.m. of the next day the amount of sugar in the blood of the carotid was 0·089 %. The blood vessels of both kidneys were then tied. At 4 p.m. the blood was again examined and the amount of sugar was found to be 0·078 %.

Exp. II. Dog, 5·6 ks. in weight. The carotid blood in its normal state contained 0·170 % of sugar. 0·75 gr. of phloridzin was injected. On the next day the amount of sugar in the blood was 0·109 %. The dog had eliminated in the meantime 160 c.c. of urine of sp. gr. 1050 and containing

3·3 % of sugar. The blood vessels and ureters of both kidneys were ligated in the morning at 10 o'clock. At 5 o'clock p.m. the blood was again examined and 0·121 % of sugar was found.

Exp. III. Dog, 6·7 ks. in weight. The carotid blood in its normal state contained 0·101 % of sugar. 1 gr. of phloridzin was injected. On the next morning the blood contained 0·106 % of sugar. In the meantime the dog had eliminated 800 c.c. of urine of sp. gr. 1050 and containing 6·25 % of sugar. The blood vessels of both kidneys were ligated at 10 o'clock a.m.; at 4 o'clock p.m. the amount of sugar in the blood was 0·209 %.

Exp. IV. Dog, 1·56 ks. in weight. At 9 a.m. the normal carotid blood contained 0·087 % of sugar. The blood vessels of both kidneys were then ligated and 2 grs. of phloridzin were injected at once. At 5 p.m. the blood contained 0·075 % of sugar; at 9 a.m. on the next day 0·064 %.

Exp. V. Dog, 5·7 ks. in weight. The blood was tested for sugar; then the blood vessels of both kidneys were ligated and 1 gr. of phloridzin was injected immediately. The normal blood contained 0·093 % of sugar; the blood after the operation 0·093 %.

Exp. VI. Dog, 5·7 ks. in weight. 1 gr. of phloridzin was injected after ligation of the blood vessels of both kidneys.

Sugar in the blood before the operation = 0·169 %.
" " after " = 0·147 %.

Exp. VII. Dog, 1·374 ks. in weight. 1·5 gr. of phloridzin was injected after ligation of the blood vessels of both kidneys.

Sugar in the blood before the operation = 0·119 %.
" " after " = 0·102 %.

The results of the experiments may be summed up in tabular form as follows:—

Percentage quantity of sugar in blood.

Exp.	Normal blood	Blood after phloridzin	Blood after ligation of renal vessels and phloridzin
I.	0·120	0·089	0·078
II.	0·170	0·109	0·121
III.	0·101	0·106	0·209
IV.	0·087	—	0·075 0·064
V.	0·093	—	0·093
VI.	0·169	—	0·147
VII.	0·119	—	0·102

Discussing these results we find that in one case after ligation of the blood vessels of the kidneys a decrease of the quantity of sugar in

the blood took place; in two other cases, an increase. This latter result coincides with that obtained by Minkowsky and seemingly corroborates his theory. But against this theory the following objections may be raised: first, that Minkowsky himself has obtained an increase of sugar beyond the normal after the extirpation of the kidneys; consequently there is not, as he claimed, simply a restoration of sugar to its normal state; and, second, that if the essence of phloridzin glycosuria actually consists in a simple elimination of sugar from the blood, we are not to expect a decrease of sugar after excluding the kidneys from the general blood circulation by the ligation of their blood vessels, and subsequent phloridzin injection. In Experiments IV—VII, however, I obtained a decrease of sugar even when the phloridzin had been injected after the ligation of the blood vessels. The tendency of the above experiments is hence against the "elimination" theory. Further the extirpation of the kidneys or the tying of their vessels is not to be regarded as an operation that leaves the other processes of the organism in their normal state. On the contrary, the changes involved were so profound that the animals survived less than two days. Evidently from the nature of the operation we have to be very cautious in drawing conclusions. Hence, the share of the kidneys in phloridzin glycosuria must be studied by other means. And it seemed to me that a comparison of the amounts of sugar in the arterial and the venous blood of the kidneys might throw light upon the "elimination" theory.

Group B.

This group comprises the results of comparison of the amounts of sugar in the blood of the renal artery and the renal vein after the administration of phloridzin.

Exp. I. Dog, 12 ks. in weight. 1·5 gr. of phloridzin was injected. On the third day afterward another injection of 0·5 gr. was made. On the fourth day cannulae were inserted into the right renal artery and the left renal vein, and blood was drawn for examination.

Amount of sugar in the arterial blood = 0·136 %.
" " " venous " = 0·143 %.

Exp. II. Dog, 10 ks. in weight. 1 gr. of phloridzin was injected. On the next day the blood of the left renal artery and right renal vein was examined.

Amount of sugar in the arterial blood = 0·150 %.
" " " venous " = 0·157 %.

Exp. III. Dog, 8·8 ks. in weight. 0·5 gr. of phloridzin was injected. On the next day the blood was taken from the left kidney only.

Amount of sugar in the arterial blood = 0·098 %.
„ „ „ venous „ = 0·121 %.

Exp. IV. Dog, 21·4 ks. in weight. 2 grs. of phloridzin were injected. During the first day he eliminated 500 c.c. of urine of sp. gr. 1050 and containing 5 % of sugar; during the second day 1000 c.c. of urine of sp. gr. 1060 and containing 5 % of sugar. On the third day the renal blood was examined.

Amount of sugar in the arterial blood = 0·118 %.
„ „ „ venous „ = 0·122 %.

Exp. V. A large dog, had been unusually long under ether. 1·5 gr. of phloridzin was injected. During the first day he eliminated 1135 c.c. of urine of sp. gr. 1020 with 4 % of sugar; on the second day 100 c.c. of urine. The renal blood was examined on the third day.

Amount of sugar in the arterial blood = 0·098 %.
„ „ „ venous „ = 0·102 %.

Exp. VI. A large dog, had been unusually long under ether. 1 gr. of phloridzin was injected. He eliminated during the day 450 c.c. of urine of sp. gr. 1060 with 4·15 % of sugar. On the second day the renal blood was examined.

Amount of sugar in the arterial blood = 0·119 %.
„ „ „ venous „ = 0·121 %.

Exp. VII. Dog, 11 ks. in weight. 1 gr. of phloridzin was injected. During the first day he eliminated 420 c.c. of urine of sp. gr. 1020 and containing 5 % of sugar. During the second day he eliminated 325 c.c. of urine of sp. gr. 1060 and containing 7 % of sugar. On the third day another injection of 0·5 gr. of phloridzin was made. During the third day he eliminated 325 c.c. of urine of sp. gr. 1070 with 10 % of sugar. On the fourth day the renal blood was examined.

Amount of sugar in the arterial blood = 0·160 %.
„ „ „ venous „ = 0·155 %.

Exp. VIII. Dog, 10 ks. in weight. 1 gr. of phloridzin was injected. In the morning of the next day another injection of 0·5 gr. of phloridzin was made. In the afternoon the renal blood was examined.

Amount of sugar in the arterial blood = 0·109 %.
„ „ „ venous „ = 0·133 %.

Exp. IX. Dog, 18·5 ks. in weight. 1 gr. of phloridzin was injected. On the next morning another injection of 0·5 gr. of phloridzin was made.

During the day the dog eliminated 350 c.c. of urine of sp. gr. 1060 with 3·3 % of sugar. The renal blood was examined on the second day.

Amount of sugar in the arterial blood = 0·127 %.
„ „ „ venous „ = 0·132 %.

The results are here grouped in tabular form:

Comparison of percentage amounts of sugar in blood of renal artery and renal vein after administration of phloridzin.

Exp.	Renal arterial blood	Renal venous blood
I.	0·136	0·143
II.	0·150	0·157
III.	0·098	0·121
IV.	0·118	0·122
V.	0·098	0·102
VI.	0·119	0·121
VII.	0·160	0·155
VIII.	0·109	0·133
IX.	0·127	0·132

The theory of von Mering and Minkowsky teaches us to expect a loss of sugar from the blood in passing through the renal circulation. In the above experiments no loss occurred except in one case (Exp. VII) and this lay within the limits of error. In Experiments III and VIII on the contrary the amount of sugar in the vein was considerably greater than that in the artery. It may be possible to explain these results by the supposition that the blood after yielding part of its water for the formation of urine leaves the kidney in a more concentrated state. But I have not noticed any relation between the amount of urine eliminated and the increase of sugar in the venous blood. The results hence speak against the "elimination" theory.

I sought next to obtain more facts concerning the activity of the kidneys in the production of sugar. To this end I considered it of value to compare the amount of sugar in the kidney itself before and after the administration of phloridzin. In two cases I extirpated one kidney, then injected phloridzin, and on the next day determined the amount of sugar in the second kidney. In other animals I ascertained the amount of sugar after the injection of phloridzin only.

Group C.

This group gives the results of comparison of the amounts of

sugar in the normal kidney and in the kidney after the injection of phloridzin.

Exp.	Wt. of dog in kilos	Amount of phloridzin injected in grs.	Normal kidney		Kidney after injection of phloridzin	
			Wt. in grs.	Percentage of sugar	Wt. in grs.	Percentage of sugar
I.	8·7	1·0	43·0	0·102	35·0	0·221
II.	13·7	1·0	45·0	0·169	41·0	0·216
III.	9·2	0·75 + 0·5	—	—	40·5	0·200
IV.	11·1	1·0 + 0·5	—	—	31·0	0·550
V.	10·2 (fasting)	1·0	—	—	42·0	0·145
VI.	15·5	1·0 + 0·5	—	—	57·0	0·281

These experiments indicate that after the injection of phloridzin the amount of sugar in the kidney may be very considerable and that it is at least greater than in the normal kidney. This latter fact indicates that in relation to the elimination of sugar the kidneys do not serve as a simple filter; it can be explained only by supposing an active production of sugar by them. This is not improbable. For they may undergo the same general nutritive changes as any other tissue of the body; and Paschutin has proved by a number of experiments that a tissue or organ may undergo carbohydrate degeneration, after its nutrition has been disturbed. Even in the brain, which in its normal state contains no carbohydrates, Paschutin found a considerable quantity of glycogen after artificial inflammation. Further, as already mentioned, Ehrlich, Straus and many others have been able to prove the presence of glycogen in the kidneys in diabetes only; and Straus failed to obtain it when he experimentally produced a hyperglycaemia. There hence appears little doubt as to the active part of the kidneys in the production of phloridzin glycosuria.

But now there arises the question, whether the kidneys are the only place of increased production of sugar during the action of phloridzin, or whether other organs play a similar rôle. Theoretically either opinion is admissible. We have just cited Paschutin's experiments by which he proves the possibility of an increased production of carbohydrates by any organ. It is evident that these carbohydrates may be eliminated in the form of sugar. There are, indeed, a great many cases of glycosuria which accompany certain local diseases. Diseased kidneys may be more prone than other organs to produce glycosuria since they

eliminate sugar more directly. But, on the other hand, we cannot deny that diseased organs may produce poisons which would disturb the metabolism of the whole body so as to result in a secretion of sugar.

As to phloridzin diabetes almost all authorities ascribe to the kidneys only, as opposed to other organs, the causation of glycosuria. And von Noorden in his latest book says: "Es ist schon erwähnt, dass der Angriffspunkt des Giftes in den Nieren zu liegen scheint, dass Phloridzin sie der Fähigkeit beraubt, die normalen Zuckermengen des Blutes zurückzuhalten. Mit dieser Erkenntniss hat der Phloridzin-Diabetes die Berechtigung verloren der Zuckerkrankheit des Menschen an die Seite gestellt zu werden." But very recently Cornevin after injection of phloridzin also found an increased secretion of sugar in the milk. Consequently in phloridzin glycosuria the kidneys are not the only sugar-forming organs.

This matter can be treated satisfactorily, however, only by a study of the sugar in all the organs together with an examination of the entire metabolism of the organism.

The general metabolism during phloridzin glycosuria has been investigated. Thus von Mering and Moritz and Prausnitz have found an increased nitrogen elimination; Quinquaud and Uschinsky do not concur in this result but find nitrogen excretion rather diminished. Furthermore, it is certain that the amount of eliminated sugar is not dependent upon either the quantity or the quality of the food. Sugar appears after continuous fasting also, when the organism is impoverished in carbohydrates.

As to the chemical analysis of the tissues but little has been done in phloridzin glycosuria. The changes of glycogen in the liver and the muscles have been investigated by von Mering and Prausnitz. Lastly, as we have seen, investigations of sugar in blood have been made after the injection of phloridzin only (von Mering), after phloridzin injection and ligation of the ureters or blood vessels of the kidneys (Uschinsky), and after phloridzin injection and extirpation of the kidneys (Minkowsky). As already mentioned, von Mering after three determinations of the sugar in the blood propounded his "elimination" theory.

In order to ascertain whether phloridzin glycosuria derives its sugar simply by impoverishing the blood, or whether more profound changes take place in the tissues, I undertook some analyses of the blood. I examined the amounts of water, solids, sugar, proteids, ethereal extract containing fat, cholesterin, and lecithin.

Group D.

This group contains the results of analysis of the blood of dogs before and after the administration of phloridzin.

Exp. I. A dog, 9·8 ks. in weight, was fed daily for some days before and during the experiment with 250 grs. of meat free from fat. Some blood was taken from the carotid artery and analyzed; 1 gr. of phloridzin was then injected. On the next day another injection of 0·5 gr. of phloridzin was made. On the fourth day the blood was again examined.

The results of the analyses are shown in the following table:

	Before injection of phloridzin	After injection of phloridzin
Water	76·0 %	79·9 %
Solids	24·0 „	20·1 „
Glucose	0·161 „	0·143 „
Proteids	23·3 „	18·8 „
Serum albumen	21·0 „	15·4 „
Serum globulin	2·3 „	3·4 „
Fat, cholesterin and lecithin	0·27 „	0·33 „

Exp. II. A dog, 18 ks. in weight, received on the days before and after the first examination of blood 400 grs. of meat. After an examination of the blood 1·5 gr. of phloridzin was injected. On the next day 0·5 gr. of phloridzin was injected. On the third day the blood was again examined. The results of the analyses are as follows:

	Before injection of phloridzin	After injection of phloridzin
Water	78·6 %	78·6 %
Solids	21·4 „	21·4 „
Glucose	0·117 „	0·113 „
Proteids	21·0 „	20·0 „
Serum albumen	16·0 „	14·5 „
Serum globulin	4·8 „	5·5 „
Fat, cholesterin and lecithin	0·31 „	0·35 „

Exp. III. A dog, 21·4 ks. in weight, received about 800 grs. of meat on the days before and after the examination of the blood. After the first examination of the blood 2 grs. of phloridzin were injected. On the third day a second examination of the blood was made. The results of analyses are as follows:

	Before injection of phloridzin	After injection of phloridzin
Glucose	0·114 %	0·121 %
Proteids	21·3 „	20·8 „
Serum albumen	16·95 „	13·0 „
Serum globulin	4·35 „	7·8 „
Fat, cholesterin and lecithin	0·4 „	0·3 „

Exp. IV. A dog, 16·5 ks. in weight, received before the examination 280 grs. of meat. After the first examination of the blood 1·5 gr. of phloridzin was injected. On the next day the dog received 120 grs. of meat; on the third day 250 grs. Here are the results:

	Before injection of phloridzin	1 day after injection of phloridzin	2 days after injection of phloridzin
Glucose	0·210 %	0·131 %	0·223 %
Proteids	22·0 „	16·6 „	19·5 „
Fat, cholesterin and lecithin	0·36 „	0·39 „	0·36 „

Exp. V. A dog, 10·6 ks. in weight, fasted two days before and during the experiment. After the first examination of the blood 1·5 gr. of phloridzin was injected. Here are the results:

	Before injection of phloridzin	1 day after injection of phloridzin	2 days after injection of phloridzin
Glucose	0·150 %	0·114 %	0·150 %
Proteids	22·85 „	19·3 „	—
Fat, cholesterin and lecithin	0·29 „	0·33 „	—

Summing up the results of the above experiments and comparing them with those found for spontaneous diabetes, we find by experiment with phloridzin almost a constant decrease of the general amount of proteids and a varied relation between the serum albumen and the serum globulin. Serum albumen is usually decreased in quantity; serum globulin increased. These results are important inasmuch as they tend to show increased decomposition of the proteids in the body. This relation is also observed in fasting. The possibility of fasting in the above cases is excluded, however, by the fact of food having been given to the animals throughout the experiment, except in No. V.

The ethereal extract containing fat, cholesterin, and lecithin is in most cases increased, which again agrees with spontaneous diabetes (Jaksch, Gamgee).

As to the substance most essential to diabetes, the sugar, I have, like others, frequently found some decrease of it in the blood. But this is

by no means constant; and there are also cases of increase of sugar. (See Exps. III and IV.) It is also true that the fluctuation of the amount of sugar in either direction, is in most cases very slight. In my opinion it is difficult to explain phloridzin glycosuria by hyperglycaemia, as it is difficult to explain it by the mere extraction of the sugar from the blood. Such explanations are all the more improbable since the decrease of sugar in the blood is not proportional to the quantity of the sugar eliminated by the urine, as we might have expected, if we accepted the "elimination" theory. On the other hand we do frequently observe that a relatively higher amount of sugar in the blood is accompanied by its increased elimination in the urine. But increased glycaemia is not a necessary concomitant of spontaneous diabetes. "Es ist nicht richtig dass die gesteigerte Glykaemie eine nothwendige Bedingung für die Glycosurie ist," says Seegen. This opinion he bases upon an examination of a considerable number of patients suffering with diabetes, whose blood did not contain an amount of sugar above the normal. Consequently in this respect phloridzin glycosuria does not differ from what is observed in *diabetes mellitus.*

Thus the general analysis of the blood seems to show that phloridzin glycosuria does not originate simply in the extraction of sugar from the blood, but that more profound changes in the tissues take place, and that these changes corroborate the views of those authors who see the source of sugar in phloridzin glycosuria in the decomposition of proteids. The absence of hyperglycaemia may be explained by the supposition that the organism has not lost its ability to rid itself of the superabundance of sugar; on the one hand by its elimination through the kidneys, and, on the other, by its increased decomposition. In favour of the latter supposition may also be construed the increased quantity of the ethereal extract, which may be regarded as possibly the product of the decomposition of sugar; and also the fact that the decrease of sugar sometimes takes place even when phloridzin is injected after the ligation of the renal blood vessels. It may also be observed that if phloridzin glycosuria represented simply the decrease of sugar in the organism, it would present symptoms characteristic of carbohydrate inanition only and it would be difficult to explain the rest of its symptoms.

Conclusions.

Thus we are confronted with two views on the origin of phloridzin diabetes. Some think it the result of a simple elimination of sugar

from the organism by the kidneys; others see in it an excessive formation of glucose.

The first base their view on the slight decrease of sugar in the blood after the injection of phloridzin and on the fact that after the extirpation of the kidneys the quantity of sugar in the blood is somewhat increased in some cases. But no one has succeeded in establishing a fixed relation between the quantity of sugar in the blood and the sugar eliminated. Furthermore I have obtained a decrease of sugar in the blood in some cases when the phloridzin was injected after ligation of the renal vessels. Finally, as demonstrated by Cornevin, the phloridzin greatly increases the quantity of sugar eliminated by the milk. Consequently this poison does not affect the kidneys only. The operation of extirpation of the kidneys can scarcely be considered as decisive of the question of the origin of the glycosuria.

As to the second view, that there is an increased production of sugar, and that more especially by the kidneys, I may contribute the facts that the venous blood of the kidneys in phloridzin glycosuria contains in some cases more sugar than the arterial, and that the quantity of sugar in the kidney tissue itself increases after the injection of phloridzin.

Finally, the composition of the blood in phloridzin diabetes testifies to the decomposition of proteids rather than to the mere elimination of sugar.

I deem it a pleasant duty to express my thanks to Prof. J. G. Curtis and Dr. F. S. Lee for the privilege of their laboratory and for the help extended to me during my work.

BIBLIOGRAPHY.

Abeles, Med. Centralbl. 1885.
Armani (quoted from Straus).
Cornevin, Comp. rend. CXVI. 6, p. 263.
Ebstein, Deutsches Arch. f. klin. Med. XXIII. 1881.
Ehrlich, Zeitschr. f. klin. Med. VI. 1883.
Farraro, Il Morgagni, 1883 (quoted from Straus).
Fichtner, Virchow's Archiv, CXIV. 1888.
Gamgee, Phys. Chem. of the Animal Body, I.
Grohe, Griefswald. med. Beiträge, 1865.
Jaffe, Virchow's Archiv, XXXVI. 1866.
Jaksch, Zeitschr. f. klin. Med. XI. 1886.
Kaufmann, Semaine Méd. 1894.

Kühne, Virchow's Archiv, xxxii. 1865.
Krawkow, "Vratch," 1890 (Russian).
Külz and Wright, Zeitschr. f. Biol. xxvii. 181, 1890.
v. Mering and Minkowsky, Arch. f. exper. Path. und Pharm. xxvi. 1889.
v. Mering, Med. Centralbl. 1885.
v. Mering, Zeitschr. f. klin. Med. xiv. 1888.
Minkowsky, Arch. f. exper. Path. und Pharm. xxxi. 1893.
Moritz and Prausnitz, Zeitschr. f. Biol. xxvii.
v. Noorden, Lehrb. d. Path. des Stoffwechsels, Berlin, 1893.
Panormow (quoted from Uschinsky).
Paschutin, Course of Gen. and Exp. Path. v. 1, Part 1 (Russian).
Pollatschek, Zeitschr. f. klin. Med. 1887.
W. Porter, The New York Med. Jour. 1885.
Prausnitz, Zeitschr. f. Biol. xxix.
C. Schmidt (quoted from Paschutin).
Straus, Arch. de Physiol. 1885.
Thiel, Arch. f. exper. Path. und Pharm. xxxiii. 1887.
Uschinsky, "Respiration and Calorimetry in Phloridzin Glycosuria," 1890, St. Petersburg (Russian).
Vernois, Arch. gén. de Méd. 1853.
Wolkow, "Klinicheskaya Gazetta," 1889 (Russian).