Adler (I.)

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Oxaluria and its Relations to Certain Forms of Nervous Disease

BY

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Oxaluria and its Relations to Certain Forms of Nervous Disease.[1]

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EVER since Prout[2] in 1820 first called attention to the occurrence of oxalic acid, principally as oxalate of lime, in the urine of persons suffering from a variety of diseases, and in later publications sought to establish oxaluria as a disease *sui generis* and characterized by well-marked symptoms, the excretion through the urine of oxalic acid in health and in disease has been a subject of much discussion. While Prout based his assumptions rather on hypothesis than on facts, Golding Bird[3] first demonstrated the occurrence of oxalate of lime crystals in the urine, which indeed had been seen and described by Brugnatelli in 1787, but not recognized by him as to their true chemical composition.

Numerous investigators took up the subject, and in England at least oxaluria obtained a place of its own in the nosological system. The symptoms were chiefly disturbances of the nervous and digestive systems. Mental depression, tædium vitæ, headaches, neuralgic pains, especially in the back and in the limbs, tremor, insomnia, impairment of vision even to complete amaurosis, loss of

[1] Read before the New York Neurological Society, January 3, 1893.

[2] For a very complete survey of the older literature on oxaluria, see Smoler, Studien über Oxalurie. Prager Vierteljahresschrift, xviii. Jahrg., Bd. i. & ii.

[3] Lectures on Physiological and Pathological Characters of Urinary Deposits. 1846.

appetite, constipation, emaciation, are some of the many symptoms claimed as characteristic of this disease; the physical sign, the occurrence of more or less oxalate crystals in the urine.

In France the theory of oxaluria could not obtain a sure footing, and it was principally Gallois[1] who, after most careful investigation of the urine of healthy and of sick persons, maintained the temporary occurrence of oxalate of lime in the urine of perfectly healthy subjects of all ages and both sexes. He showed, furthermore, that oxalate sediments can occur in the most varied forms of disease and also after ingestion of certain kinds of food and certain drugs. Similar results were obtained by Bence-Jones.[2]

In Germany, Lehmann,[3] and especially Beneke,[4] studied the occurrence of oxalate of lime in the urine under the most varied conditions, and also came to the conclusion that oxalic acid is excreted under manifold conditions of disease, and that oxaluria as a distinct nosological type does not exist. A like result was reached by Smoler[5] who studied the urine in a very large number of persons suffering from all kinds of disease.

It is well to note here that all these investigations were made mainly with the microscope. The urine was allowed to stand for twenty-four hours or longer, and the sediment then examined for oxalate of lime crystals. A rough estimate of their number and size as they appeared in the microscopic field was considered all that was needed. After the studies of Beneke[6] and Neubauer,[7] who showed that acid sodic phosphate when present in the urine will hold the oxalate of lime in solution and prevent its sedimentation, it was frequently found neces-

[1] Mémoir sur l'oxalate de chaux dans les sédiments de l'urine, dans la gravelle et les calculs. Soc. de Biologie, 1859.
[2] Medico-Chirurgical Transactions, vol. xvii.
[3] Lehrbuch der physiol. Chemie, 1850.
[4] Zur Physiologie und Pathologie des phosporsauren, und oxalsauren Kalks. 1850.
[5] Loc. cit.
[6] Loc. cit.
[7] Archiv für gemeinschaftl. Arbeiten, Bd. iv., 1856. Ueber Oxalsäurebildung.

sary to add certain chemicals (calcium chloride and acetic acid) before making the microscopical examination. Though this rapid procedure gives results incomparably more trustworthy than the older and simpler method, it is nevertheless at best but a rough approximation and can in no wise take the place of exact quantitative determination.

All these investigations, and other and more exact ones, to which I shall have briefly to refer later on, while they opened up many new lines of research and left many points of fundamental importance unsettled, nevertheless appeared to establish one fact beyond doubt: the non-existence of oxaluria as an independent type of disease. Some years ago, however, Cantani[1] again raised the standard of oxaluria. On the basis of a number of clinical histories, the microscopic examination of the chemically prepared urine, and the effect of certain therapeutic measures, he elaborates an extremely plausible theory of the excretion of oxalic acid under normal and morbid conditions.

His theory it briefly this: Under normal conditions mainly such oxalic acid appears in the urine as is directly introduced into the system with the food. Under abnormal conditions the excreted oxalic acid may be derived from incomplete oxidation of the proteids; of uric acid and—and this is, according to Cantani, the principle source of pathological oxaluria—from incomplete oxidation of the carbohydrates. He asserts that when the system has been overcrowded for a length of time with an excess of carbohydrates, the organs and tissues whose duty it is to gradually transform these substances into the ultimate products of oxidation—water and CO_2, become in a measure exhausted and are rendered incapable of carrying oxidation further than the oxalic acid stage. An excess of oxalic acid, in the shape chiefly of oxalate of lime, is thus thrown into the blood and voided into the kidneys and urine, and morbid symptoms

[1] Specielle Pathlogie und Therapie der Stoffwechsel-krankheiten. Deutsch von Dr. Hahn, Bd. II., Berlin, 1880.

necessarily follow. That oxaluria does not follow in every instance of habitual abuse of carbohydrates, nor even in the majority of cases, is explained by Cantani on the assumption of individual predisposition, in which heredity, lesions of the digestive and nervous systems, corpulency, and indolent and pampered modes of living are leading factors.

It is interesting to note the parallelism of this view of oxaluria with the same author's theory of diabetes; the difference between the two diseases being mainly this, that in diabetes mellitus the exhausted tissues cannot tranform sugar at all, and it is voided as such; in oxaluria sufficient energy remains to transform the carbohydrates as far as the oxalic acid stage.

Cantani himself has not infrequently found oxaluria a concomitant of diabetes, and, in several instances in the case of diabetic patients, oxaluria alternating with glycosuria. Similar and very exact observations have been recorded by Fürbringer.[1]

The symptoms of pathological oxaluria are, according to Cantani, manifold, but in their aggregation sufficiently characteristic to admit of certain diagnosis. First and foremost is the excess of oxalate of lime in the urine, when not due to direct ingestion of oxalic acid with the food. This excess Cantani estimates by the aid of the microscope, but does not determine it by exact quantitative analysis. In a number of instances he succeeded by a complicated procedure[2] in obtaining oxalate of lime crystals from the blood serum. Prominent among other symptoms are those relating to the nervous system: mental depression, melancholia to the verge of suicide, extreme nervous irritability, impairment of memory and intellectual vigor, insomnia, sexual impotence, etc. Besides these and other nervous symptoms there are always disturbances of the vegetative functions. In almost all cases more or less rapid emaciation, loss of appetite, dyspeptic symptoms, such as eructations, flatulence, consti-

[1] Zur Lehre von Diabetes mellitus. Deutsches Archiv f. klin. Medicin, Bd. xvi., 1875. [2] Loc. cit., p. 8.

pation, etc. In most of these cases there was dull pain in the back and in the region of the kidneys, and quite a number at various times passed oxalate gravel or calculi.

The therapeutic measures consisted, in all cases, in the enforcement of an absolute milk and meat diet, with alkaline waters as a drink.

Under the influence of this diet which was maintained for weeks and even months, nearly all patients rapidly recovered. The oxalate disappeared from the blood and urine and did not reappear, when, in the course of time, a mixed diet was again permitted. With the disappearance of the oxalate in the urine the patients regained flesh and recovered their normal healthy functions of the digestive and nervous organs. Those few that were not entirely cured, either owing to remissness in diet or because they withdrew from observation, were, nevertheless, materially improved.

It is not my object to enter into a detailed criticism of Cantani's most interesting and suggestive work. Permit me only very briefly to state a few of the objections that can be advanced.

In the first place, the absence of quantitative determinations leaves the whole superstructure of ingenious speculation without a solid foundation of facts comparable among themselves or with other similar ones. Furthermore, none of the other important constituents of the urine, such as urea and uric acid, have, it would appear, been taken into account. And yet it seems that these also, especially in cases of emaciation and grave metabolic disturbance, should claim a most careful consideration. Again, the clinical histories are not sufficiently detailed and explicit, and might often be construed in quite a different sense from that adopted by the author. The demonstration of a few oxalate crystals in the blood serum should be accounted a proof of pathological oxalæmia only after it has been established by numerous experiments that the like can never be found in healthy persons. Oxalate gravel and calculus can by itself not be accepted as proof of excess of oxalate in the urine, inasmuch as local tissue

changes in kidney and bladder may cause local precipitation without absolute excess (Hoppe-Seyler), as is the case too with uric-acid calculus.

Lastly, and most important of all, it appears to me that Cantani has failed to show that the grave disturbances, particularly in the functions of the nervous and digestive systems, are due to the excess of oxalic acid as a primary cause. It is quite possible that under certain conditions very serious changes can take place in the ordinary metabolism of the system, as one of the results of which an excess of oxalic acid appears in the urine. That nervous disturbances or digestive lesions may possibly be the cause of these metabolic changes and the excess of oxalic acid an effect or only an incidental symptom, and perhaps an innocuous one, is by no means disproven. Nor is the effect claimed for the absolute meat and milk diet incompatible with this latter hypothesis. It is in considering these questions that the want of quantitative determination is most seriously appreciated.

If now we endeavor to ascertain what is the actual knowledge we possess at present concerning the excretion of oxalic acid and the physiological data relating thereto at our command, we will find a rather unsatisfactory state of affairs. On very few even of the fundamental points has unity of opinion been obtained, while the very large majority of questions pertaining to this subject are still enveloped in obscurity and doubt. It is certain that most plants and nearly all vegetables used for food contain oxalic acid; some of the latter, like tomatoes, rhubarb, rumex, bananas, apples, spinach, carrots, etc., a comparatively large percentage. It seems tolerably certain also, especially through the experiments of Gaglio,[1] that all or very nearly all the oxalic acid thus taken into the system reappears again untransformed in the urine, and some perhaps in the fæces, principally as oxalate. From this it follows that oxalic

[1] Ueber die Unveränderlichkeit der Kohlenoxyds und der Oxalsäure im thierischen Organismus. Archiv für experimentelle Pathologie und Pharmacologie, Bd. xxii. 1886 and 1887.

acid can and does occur in the urine of perfectly healthy persons, and that it may occur in quite large quantities if the diet is one rich in oxalic acid. On this point all authors are now agreed.

Is oxalic acid a constant component of the normal urine, like urea and uric acid? Is the oxalic acid in the urine due altogether to oxalic acid ingested, or are there chemical transformations and reactions normally going on which result in the production of certain, perhaps very minute, quantities of oxalic acid? These questions have been much discussed, but still await a conclusive answer. The fact that oxaluric acid ($C_3H_4N_2O_4$) has been found in normal urine [1] and that Auerbach [2] found oxalic acid in traces in the urine of dogs that were fasting, would seem to indicate that oxalic acid may originate in the course of normal metabolism. Even the fundamental question, What are the normal quantitative limits of oxalic acid excretion in the urine? has not been satisfactorily settled. Schultzen,[3] working with a method of his own, found an average of 0.1 in twenty-four hours. Fürbringer [4] undertook a large and most laborious and exact series of analyses after Neubauer's method. He found that, while the normal urine could contain mere traces, *i.e.*, less than 0.001 *pro die*, the normal maximum should be placed at not more than 0.02. In a later investigation in which he modified his method, Schultzen [5] established an average of from 0.02 to 0.07 as about normal. Salkowski [6] found in a perfectly healthy man 0.144. Latterly the subject has again been investigated by Wesley Mills [7] who, after a careful comparison of the methods of Neubauer and Schultzen, finds the results after Neubauer's method uniformly too small and the figures obtained according to Schultzen as approximately correct.

[1] Schunk, Journal f. prakt. Chemie, Bd. 100, p. 125.
[2] Zeitschr. f. klin Medicin, Bd. ii.
[3] Reichert u. Du Bois-Reymond's Archiv, 1868, pp. 719 and 720.
[4] Zur Oxalsäureausscheidung durch den Harn.
[5] Zeitschrift f. Analyt. Chemie, Bd. viii., p. 521.
[6] Virchow's Archiv, Bd. lii., p. 64. 1871.
[7] Virchow's Archiv, Bd. IC., 1885, p. 305 et seq. "Ueber die Ausscheidung der Oxalssäure durch den Harn."

As regards the other questions hinted at above, still less unanimity obtains among investigators. It has long been ascertained that uric acid ($C_5H_4N_4O_3$) under the influence of artificial oxidation, before finally being resolved into carbonic acid and water, will give as intermediate products urea (CON_2H_4) and oxalic acid ($C_2H_2O_4$). This fact gave rise to the very plausible and at one time generally accepted theory that under pathological conditions oxalic acid in the urine resulted from incomplete oxidation of uric acid. In support of this theory Frerichs and Wöhler asserted that introduction of uric acid into the stomach was followed by increase of oxalic acid in the urine; an assertion which the very careful experiments of Fürbringer could not substantiate. As a necessary consequence of this theory it was claimed by many authors that an excess of oxalic acid in the urine is found in such diseases as are accompanied by disturbances of the respiratory system and increase of carbonic acid in the blood, and in which, therefore, the oxidations are supposed to be diminished. (Pneumonia, phthisis, emphysema, valvular lesions of the heart, etc., etc.) We shall see that careful analysis furnishes no basis for these assumptions. The fact that uric acid can be separated into urea and oxalic acid in the test-tube by no means proves that this ever actually occurs in the living body. It is not impossible that oxalic acid can be derived from proteids, so, according to Kühne, from kreatine. On the other hand, the slow oxidation of sugar with uric acid can also produce oxalic acid, and Cantani, as we have seen, bases his entire theory on the assumed derivation of oxalic acid from the incomplete oxidation of the carbohydrates. The experiments bearing on these questions are comparatively very few and altogether unsatisfactory. So, for instance, while Burggrave, on the one hand, finds no oxalic acid whatever in the urine of dogs fed exclusively on meat, and sees the oxalic acid appear on the addition of even minute quantities of sugar to the meat, Wesley Mills, on the other hand, finds most oxalic acid (11.1 milligr. on the average) when the dogs are fed

Number.	Name, disease, etc.	Date.	Quantity of urine in 24 hours.	Specific gravity.	Reaction and acidity.	Microscopic examination.	Urea.	Uric acid.	Relation of uric acid to urea.	Oxalic acid.	Phosphoric acid.	Chlorides.	Albumin.	Sugar.	Remarks.
1	Mr. N. H., age 63 years; melancholia, etc.	Sept. 30, 1889.	900	1.024	Acid.....	Urates and triple phosphates.	30 = 3 %....	.....	.....	0.135	.....	.....	.....	.....	.....
2	Mr. N. H., age 63 years; melancholia, etc.	Jan. 15, 1890.	1,200	1.024	Acid, 2.5.....	Oxalate octahedra numerous.	30 = 2.5 %..	0.6	1 : 50	0.050	.....	.....	.....	.....	.....
3	Mr. N. H., age 63 years; melancholia, etc.	March 5, 1890.	1,000	1.028	Strongly acid, 3.15.	Negative	35 = 3.5 %..	0.5	1 : 70	0.010	.....	.....	.....	.....	Indican.
4	Mr. N. H., age 63 years; melancholia, etc.	April 5, 1890.	1,250	1.022	Very acid, 3.9.	Oxalate crystals...	32.5 = 2.6 %	1.1	1 : 29½	0.035	... ..	.....	.....	.....	.....
5	Mr. B., age 26 years; neurasthenia.	Sept. 30, 1889.	1,200	1.021	Acid.....	No sediment.....	26.4 = 2.2 %.	.....	.....	0.422	.....	.....	.....	.....	.....
6	Mr. B., age 26 years; neurasthenia.	Oct. 14, 1889.	1,370	1.028	Very acid, 5 ..	Large and numerous oxalate crystals.	46.5 = 3.4 %	0.7	1 : 66	0.46	.....	.....	.....	.....	.....
7	Mr. B., age 26 years; neurasthenia.	Nov. 4, 1889.	1,000	1.030	Acid, 2.89	Oxalate crystals...	40 = 4 %....	.....	.....	0.063	.....	.....	.....	.....	.....
8	Mr. B., age 26 years; neurasthenia.	Nov. 27, 1889.	1,200	1.026	Very acid, 3 ..	.....	43.2 = 3.6 %	.....	.....	0.012	.....	.....	.....	.....	.....
9	Mr. B., age 26 years; neurasthenia.	Dec. 20, 1889.	1,200	1.027	Acid	.....	32.4 = 2.7 %	0.48	1 : 67	0.056	.....	.....	.....	.....	.....
10	Mr. B., age 26 years; neurasthenia.	Jan. 17, 1890.	1,450	1.026	Acid, 2.9	No sediment.....	40 = 2.8 %..	1.0	1 : 40	None.	.....	.....	.....	.....	.....
11	Mr. B. C., age 52 years; neurasthenia.	Nov. 6, 1889.	900	1.020	Acid, 2.5	Uric acid crystals.	19.8 = 2.2 %	0.33	1 : 59.4	None.	.....	.....	.....	.....	Indican increased.
12	Mr. B. C., age 52 years; neurasthenia.	Sept. 16, 1889.	1,190	1.020	Slightly acid..	Urates; no oxalates.	32 = 2.7 %..	.....	.....	0.03	.....	.....	.....	.....	.....
13	Mr. S., age 25 years; neurasthenia.	Feb. 11, 1890.	2,400	1.024	Strongly acid, 4.8.	Urates; a few oxalates.	67.2 = 2.8 %	1.7	1 : 39	0.06	.....	.....	.....	.....	.....
14	Dr. T., age 47 years; melancholia.	Feb. 19, 1891.	1,350	1.020	Acid, 3.....	.....	40.5 = 3 %..	0.3	1 : 135	0.017	2.0	9.9	.....	.....	.....
15	Mrs. R. M., age 28 years; anæmia; neurasthenia.	Dec. 16, 1889.	750	1.030	Acid	Oxalate crystals, few and small.	21 = 2.8 %..	0.4	1 : 52.5	0.011	.....	.....	.....	.....	.....
16	Mr. O. T., age 32 years; neurasthenia; hypochondriasis.	Nov. 14, 1892.	1,260	1.023	Strongly acid, 3.8.	Uric acid crystals.	35.3	0.25	.....	0.008	2.7	10.7	.....	.....	.....
17	Mr. M. A. J., age 48 years; tabes dorsalis.	Jan. 27, 1890.	800	1.026	Slightly acid, 1.8.	Small oxalate crystals.	24 = 3 %....	0.59	1 : 40	0.016	. ....	.....	.....	.....	.....
18	Mrs. G. M., age 60 years; gouty diathesis.	Dec. 7, 1889.	1,465	1.021	Strongly acid, 4.	Uric acid crystals.	35 = 2.4 %..	1.3	1 : 27	0.015	.....	... ..	.....	.....	.....
19	Mrs. G. M., age 60 years; gouty diathesis.	Oct. 5, 1890.	1,600	1.019	Acid	.....	.....	0.8	.....	0.017	.....	.....	.....	.....	.....
20	Mrs. G. M., age 60 years; gouty diathesis.	April 10, 1890.	1,550	1.022	Acid	Uric acid crystals.	46.5 = 3 %..	2.3	1 : 20	0.019	.....	.....	.....	.....	.....
21	K., German Hospital; typhoid fever.	Nov. 6, 1889.	1,400	1.024	Acid, 3.7	Hardly sediment..	53.2 = 3.8 %	1.8	1 : 29.5	Only trace.	.....	.....	.....	.....	Indican increased.
22	K., German Hospital; typhoid fever.	Nov. 15, 1889.	1,200	1.018	Slightly acid, 3.	No oxalate crystals.	30 = 2.5 %..	1.33	1 : 22.5	0.012	.....	.....	.....	.....	.....
23	K. (male), German Hospital; phthisis pulmon.	Nov. 29, 1889.	950	1.021	Slightly acid, 1.8	.....	22 = 2.3 %..	0.52	1 : 41.5	0.019	.....	.....	.....	.....	.....
24	W. (female), German Hospital; phthisis pulmon.	Feb. 9, 1890.	900	1.018	Acid, 1.35	....	18.9 = 2.1 %	.....	.....	0.028	.....	.....	.....	.....	.....
25	W. (female), age 12 years, German Hospital; pleuro-pneumonia; endocarditis.	March 12, 1890.	600	1.026	Acid	.....	18 = 3 %...	0.54	1 : 3.3	0.025	.....	.....	.....	Trace.	.....
26	N., German Hospital; carcinoma hepatis.	Feb. 20, 1890.	1,550	1,014	Acid, 2.5	.....	24.8 = 1.6 %	0.9	1 : 27.5	0.007	.....	.....	....	.....	.....
27	Mr. A., age 72 years; carcinoma flexuræ sigmoideæ.	March 13, 1890.	1,170	1.022	Strongly acid.	.....	35 = 3 %....	.....	....	0.80	.....	.....	..... .	.....	Indican increased.
28	E. (female), German Hospital; cat. gastric. chron.	March 3, 1890.	1,150	1.011	Slightly acid, 0.36.	No crystals	14.9 = 1.3 %	Mere trace.	.....	None.	.....	.....	Trace.	.....	.....
29	Mrs. J. E. A., age 38 years; healthy, occasional renal colic.	Jan. 4, 1890.	1,600	1.016	Acid	Negative	35.2 = 2.2 %	0.29	1 : 120	Mere trace.	.....	.....	. .....	.....	.....
30	Mrs. W., age 85 years; cystitis; pyelitis.	Nov. 6, 1889.	1,250	1.010	Neutral	Pus; no crystals..	17.5 = 1.4 %	.....	.....	None.	.....	.....	Present.	.....	.....
31	Mr. H. A. S., age 35 years; healthy, urethritis.	Oct. 6, 1890.	1,775	1.019	Neutral	.....	50.....	1.3	1 : 38	0.001	2.5	.....	.....	.....	.....
32	Mr. H. A. S., age 35 years; healthy, urethritis.	Oct. 13, 1890.	1,400	1.030	Acid, 3.4	No crystals	42 = 3 %....	1.4	1 : 30	0.021	2.1	14.7	.....	.....	.....
33	Mr. H. A. S., age 35 years; healthy, urethritis.	Dec. 1, 1890.	1,500	1,028	Acid, 2.5	No crystals	31.5	2.9	1 : 10.8	0.0075	2.0	13.0	.....	.....	.....
34	Mr. O. M., age 45 years; cat. intest. chron.	Oct. 20, 1889.	1,200	1.022	Acid, 3.75	Uric acid crystals.	43.2 = 3.6 %	1.5	1 : 28.8	0.080	.....	.....	.....	.....	Indican increased.
35	Mr. O. M., age 45 years; cat. intest. chron.	Dec. 2, 1889.	1,150	1.020	Acid	.....	33 = 2.6 %..	.....	.....	0.060	.....	.....	.....	.....	No indican.
36	Dr. K., age 45 years; renal hemorrhage occasionally.	Oct. 28, 1890.	2,000	1.022	Acid, 1.4	Phosphate crystals.	48 = 2.4 %..	Trace.	.....	0.020	2.8	... ..	.....	.....	.....

exclusively on meat, less (5.4 milligr.) when fed on meat and increasing quantities of bread. I do not propose to enter here into chemical and physiological details, nor to attempt to unravel the contradictions and obscurities with which all these fundamental questions are beset. I desire simply to ascertain whether, on the basis of careful quantitative analyses, any relations can be established between certain forms of disease, particularly of the nervous system, and the excretion of oxalic acid in the urine. My most sincere thanks are due to Dr. E. Rosenberg, of this city, to whose skill and scientific enthusiasm I am indebted for all the analyses made use of in this investigation. The method we employed was that of Schultzen.[1] In all cases the twenty-four hours' quantity was examined. In the majority of cases the acidity was determined by titration with $\frac{1}{10}$ normal alkali solution, and expressed in grammes of oxalic acid for the entire quantity. Nearly always a careful microscopical examination was made. In all cases the urea and uric acid were determined, besides oxalic acid. Every urine was examined for albumin and sugar, and in a number of instances phosphoric acid and the chlorides were also determined (see Table of Analyses).

We will now briefly review the cases and consider in the first place the nervous disturbances.

Mr. N. H—— (Table, Nos. 1, 2, 3, 4), about sixty-three years of age, when first seen by me complained of great nervous depression, increasing frequently to paroxysms of downright melancholia; sleeplessness, occasional rheumatic pains in the back and limbs, various dyspeptic symptoms, such as loss of appetite, eructation and distress after meals, constipation, loss of weight. A brother of Mr. H—— had died of general paresis, and the haunting dread of brain disease irresistibly overpowered our patient in his spells of depression. Though always "nervous," he had never had any serious physical

[1] Loc. cit., and E. Rosenberg, Quantitative Bestimmung der Oxalsäure im Harn. N. Y. Medicinische Monatsschrift, Bd. iii., 1891, p. 484.

illness. Syphilis was denied absolutely. He had always been a lover of the good things of the table and fond of sweets and many vegetables. He never drank to excess, but was fond of champagne and good wines with his meals. Repeated and careful examination failed to detect any evidence of organic lesion of any kind. His urine was rather concentrated, acid, free from albumin and sugar, but showed under the microscope numerous large and small oxalate of lime crystals. Here, then, was a case in all essential respects identical with the cases reported by Cantani as pathological oxaluria, and it was determined to investigate it analytically. The first analysis showed only 900 c.c. for twenty-four hours' quantity, specific gravity of 1.024, acid reaction, a sediment consisting of urates and triple phosphates, 30 grammes of urea and 0.135 of oxalic acid. It is possible that, owing to some mishaps in the manipulation, the figures for the oxalic acid may have turned out too large; nevertheless there was a decided excess, and I am willing, for the sake of further discussion, to accept the figures as correct. The patient was put on Cantani's diet: sweets, vegetables, and amylaceous matter were strictly prohibited, and instead of wines he drank alkaline waters. Nevertheless the patient did not improve until ordered away from the city, when he rapidly regained spirits and sleep. On January 15, 1890, the urine was 1,200 ctgms. for twenty-four hours, specific gravity 1.024, acid 2.5, showed under the microscope numerous octahedra, urea three per cent.; uric acid, 0.6; oxalic acid, 0.05. This amount comes well within Schultzen's normal limits. The patient felt well and had not kept very strictly to his diet. About six weeks later Mr. H—— had one of the worst paroxysms of melancholia that he ever passed through. All the symptoms above detailed were exaggerated to the utmost, and well-marked suicidal tendencies were noted. An analysis made during that time showed only 0.01 of oxalic acid, but a decided increase in the urea. A still later analysis, after the paroxysm had passed and Mr. H—— was feeling tolerably well, showed 0.035 of oxalic

acid, but a very marked increase (1.1) of uric acid. These figures evidently give no basis to the assumption of a direct connection between the excretion of oxalic acid and the nervous symptoms in this case. We evidently have here a case of general neurasthenia with hypochondriacal and melancholic paroxysms based perhaps on slight hereditary taint. That certain morbid metabolic changes were going on is shown by the urea and uric acid determinations. Nevertheless the quantities of oxalic acid, with the exception of the first analysis, kept well within the normal, though, if the microscope had been relied on, an excess would no doubt have been assumed. Let me add that for the last two years the patient has been abroad, and that, while attention is no longer paid to the oxalic acid in the urine, he has been very beneficially influenced by absence from business and the diversion of travelling. Though, at rare intervals, still slightly nervous, he has gained in weight, enjoys himself thoroughly, and considers himself a healthy man.

Mr. B——, aged twenty-six. Loss of appetite, loss of sleep, distress after meals, all sorts of rheumatoid pains, particularly in the back and in the loins, emaciation, mental depression, loss of intellectual vigor and of sexual desire, general debility. Has complained of these symptoms for several years; no syphilis, no organic lesion of any kind. (Table, Nos. 5, 6, 7, 8, 9, and 10.) The first analysis gave 0.422 oxalic acid in 1,200 c.c. This amount is manifestly too large, owing to an accident in the manipulations. The second analysis again showed 0.46 oxalic acid. This may be also too high a figure, but we will assume a very decided excess of oxalic acid, especially as the urine was very acid (5), and showed large and numerous oxalate octahedra under the microscope. Particular attention is called to the amount of urea, which in this analysis was 46.5. The patient was put on a diet that had no special reference to oxalic acid. He was permitted to eat certain kinds of farinaceous food and vegetables. In the next analysis the oxalic acid amounted to 0.063, while the urea was forty per cent., equal to four per cent.

of the day's quantity. The next analysis gave only 0.012 of oxalic acid, and 3.6 per cent. of urea. A month later oxalic acid had risen again to 0.056, while urea had come down to 2.7 per cent. Four weeks later again, oxalic acid was none; urea, 2.8 per cent.; uric acid, 1.0. During all this time the condition of the patient was about the same, sometimes a little better, sometimes a little worse, but manifestly independent of the variation in the amount of oxalic acid. It was a clear case of general neurasthenia and hypochondriasis with nervous gastro-intestinal disturbances. The morbid metabolism in this case is undoubtedly to be measured by the increase in urea and uric acid, and has no relation to the oxalic acid. In this case, too, dependence on the microscope alone would have led to the assumption of an excess of oxalate, where analysis showed normal quantities.

Mr. B. C—— (Table, Nos. 11 and 12), aged fifty-two. Neurasthenia of many years' standing, without any organic lesion. Shows symptoms more especially of cerebral and spinal neurasthenia, vertigo, pains in limbs, pains in back, loss of sexual power, muscular weakness, together with gastro-intestinal symptoms, such as loss of appetite, distress after eating, diarrhœa alternating with constipation, etc. His diet consists principally of meat and milk food, and small quantities of farinaceous substances. The first analysis gave no oxalic acid, but indican abnormally increased, the second analysis, 0.03 of oxalic acid.

Mr. St—— (Table, No. 13). Neurasthenia mainly of cerebral type. Frequent headaches. Intellectual apathy, impairment of memory, great mental depression. No evidence whatsoever of organic disease. One analysis, specific gravity, 1.024, strongly acid (4.8). Microscope shows urates and oxalates. Urea, 2.8 per cent.; uric acid, 1.7; oxalic acid, 0.06.

Dr. T—— (Table, No. 14), aged forty-seven. Organically perfectly sound. Periodic melancholia of very severe type. The attacks sometimes last many months, during which the patient is tortured by almost irresistible

suicidal impulses. In this condition, insomnia, general debility, loss of appetite, and emaciation. One analysis, during acme of a paroxysm. Urine strongly acid (0.3), three per cent. of urea, only 0.3 uric acid, and 0.017 oxalic acid.

Mrs. R. M——, aged twenty-eight (Table, No. 15). General anæmia with well-marked hysterical tendencies; no organic lesion. Microscope shows small oxalate crystals; oxalic acid, 0.011.

Mr. O. T——, aged thirty-two (Table, No. 16). Nervous dyspepsia and diarrhœa; well-marked agoraphobia; rapid emaciation; no organic lesion; mixed diet; acidity, 3.8; urea, 35.3 per cent.; oxalic acid, 0.008.

Mr. M. A. J——, aged forty-nine (Table, No. 17). Tabes dorsalis of ten years' standing, with frequent gastric crises; acidity, 1.8; urea, three per cent.; uric acid, 0.59. Microscope shows numerous small oxalate octahedra. Oxalic acid, 0.016.

In all these cases it is shown that the oxalic acid, whether increased, whether within normal limits, or even if diminished, had no demonstrable influence on the course of the disease, and that emaciation or other metabolic disturbances can be accounted for by tissue waste as measured by the excretion of urea and uric acid.

Besides these cases of nervous disturbance, analyses were obtained of the urine of perfectly healthy persons, as well as of such suffering from various acute and chronic diseases, with the view of studying oxalic-acid excretion under varied conditions. I will not enter upon all of them in detail, as they can be found in the annexed table. I will single out only a few of the more important ones. As much has been said concerning the relations of oxaluria to gout, it will be interesting to note the case of Mrs. G. M——, aged sixty (Table, Nos. 18, 19, and 20), a very corpulent lady, with well-marked gouty diathesis. During the year in which the analyses were obtained, her diet consisted of a limited quantity of meat, small quantities of amylaceous food, no sweets, no pastry, a moderate amount of vegetables and fruit, and alkaline

drinks. She took also a nightly dose of rhubarb, according to her custom for many years. The analyses show a marked increase in the quantity of uric acid, but only very small quantities of oxalic acid (0.015, 0.017, 0.019), certainly referable in this case only to oxalic acid ingested with food and rhubarb.

Two analyses from a hospital case of typhoid fever (Table, Nos. 21 and 22), the first at a time when the temperatures were decreasing, but before they had reached the normal; the second during convalescence. The diet at the time of the first analysis consisted only of milk and gruel. The oxalic acid was none, but a marked increase of uric acid and urea appeared. At the time of the second analysis the diet was somewhat more liberal, as the fever had meanwhile disappeared. Oxalic acid, 0.012, and a decrease both in uric acid and urea.

Two cases of phthisis pulmonum, one male, one female, both with moderate fever (Table, Nos. 23 and 24). In one oxalic acid, 0.019; in the other, 0.028. These figures are in marked opposition to the theory which derives oxalic acid from incomplete oxidation, and confirm the results already obtained by Fürbringer and others.

A case of a child, twelve years of age, suffering from pleuro-pneumonia and valvular disease of the heart (Table, No. 25). Analysis was made at a time when febrile symptoms had disappeared and the little patient had begun to eat solids. He was, however, still distinctly cyanotic. Oxalic acid, 0.025, a result which tends to confirm the statements made in the preceding case.

A case of a woman suffering from chronic gastric catarrh with hyperacidity, on absolutely liquid diet (Table, No. 28). Oxalic acid, none.

Cancer of the liver (Table, No. 26). Moderate cachexia and very little appetite. Oxalic acid, 0.007.

Mr. A——, aged seventy-two (Table, No. 27). Cancer of sigmoid flexure; anus præternaturalis; cachexia. Principally milk diet, but eats some farinaceous and vegetable food; increase of urea (three per cent.) and of indican; oxalic acid, 0.018.

Mr. H. A——, aged thirty-five (Table, Nos. 31, 32, and 33). Strong and healthy man; has old chronic urethritis and prostatitis, in consequence of which from time to time gritty white masses, consisting principally of urates, are discharged at the beginning of micturition.

The analyses were made chiefly with a view of determining whether the local lesions favored a precipitate of oxalate. The uric acid was found very markedly increased, the oxalic acid, if anything, rather subnormal (0.001, 0.021, 0.0075).

Mrs. W ——, aged eighty-five (Table, No. 30). Chronic cystitis and pyelitis; lives almost exclusively on bread, milk, and meat; urine neutral, contains pus. No oxalic acid.

I am well aware that these observations are too few in number, and too defective in many respects, to serve as a basis for definite and authoritative general conclusions. The subject is an intensely difficult one, and our knowledge of even its elementary chemical and physiological bearings still very uncertain. Only long-continued and patient analytical and experimental work can ultimately furnish the data for a future physiology and pathology of oxalic acid in the human organism. While not pretending to solve any of the problems connected with this subject, it seems to me, nevertheless, that from the foregoing analyses and observations, as well as from the work of other observers and experimenters, the following conclusions may be provisionally deduced:

1. Oxalic acid is a normal, though possibly not a constant, constituent of the urine.

2. The amount present in a given quantity of urine can be determined with any degree of reliability only by quantitative analysis. All approximations by means of microscopic examination are untrustworthy.

3. The chief source of oxalic acid in the urine is the oxalic acid contained in the food, though it is probable that minute quantities are produced in the course of normal metabolism. Further investigation will have to

demonstrate if, and under what conditions, morbid metabolism affects the production of oxalic acid.

4. Impeded respiration, diseases of the heart and lungs, do not of themselves tend to produce an excess of oxalic acid in the urine.

5. The establishment of pathological oxaluria as a type of disease *sui generis* is not warranted by the facts at present at our command.

6. The nerve symptoms assumed as characteristic of pathological oxaluria are not caused by an excess of oxalic acid in the blood and in the urine. Analysis will show that such excess is by no means as frequent as has often been assumed.

7. Where such excess does occur not to be accounted for by ingesta, it is probably one of several symptoms of metabolic alterations primarily caused by disturbances of the nervous or digestive organs, or both, but no factor in the causation of disease.

8. In considering the excretion of oxalic acid in the urine it is of the utmost importance to take into account at the same time the excretion of the other principal constituents, particularly urea and uric acid.