Stewart (D. D.)

The author considers it altogether proper to state that Schering's Piperazin was used by him exclusively. And it may be added to prevent any misconceptions, that all other reports to date, including all those referred to herein, are based on the use of Schering's Piperazin.

PIPERAZIN

IN THE

TREATMENT OF STONE IN THE KIDNEY; REPORT OF CASES.

BY

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PIPERAZIN IN THE TREATMENT OF STONE IN THE KIDNEY; REPORT OF CASES.

PIPERAZIN, as is perhaps now generally known, is one of the more recent coal-tar derivatives. It is chemically diethylene-diamine, a piperadin in which one CH_2 group is replaced by an amide. It is freely soluble in water, and in cold aqueous solution will dissolve twelve times as much uric acid as will lithium carbonate. Its urate, which is said to be always a neutral salt, is seven times more soluble in water than is the corresponding salt of lithium, the most soluble of the metallic urates. Piperazin is a stable compound, apparently not undergoing decomposition in the organism. It is readily excreted by the kidneys, and may be detected in the urine by appropriate tests in a few hours after a single dose. The knowledge of the latter of the foregoing facts has led naturally to a wide clinical trial of piperazin in the uric acid condition, especially in gout and in uro-lithiasis, with a pretty general unanimity of opinion as to its value in uric acid gravel and calculi, although curious contradictory results are reported as to its influence upon the quality and quantity of urine. It was with a view of testing its action in cases of uro-lithiasis, and concurrently to ascertain for myself its influence upon nitrogenous excretion in the urine, that I began its trial in a number of cases of uric acid diathesis, of which I shall now only report several of suspected renal calculus in which a careful clinical examination of the remedy over quite a lengthy period was made, with accompanying thorough microscopic and chemical examinations of the urine.

It goes without saying, from what is known of the action of piperazin, that, of all conditions, uric acid gravel and stone is the one most likely to receive substantial benefit from its use. Despite the affinity of piperazin for uric acid, and the extreme solubility of its urate, little can be expected from it in uratic chronic multiple arthritic enlargement, at least in the doses generally administered,—15 grains daily. In much larger amounts, such as a drachm or two daily, exhibited over a continuous time, more promising results may be anticipated; whether, however, such doses will be tolerated without injury is yet to be determined. The present unfortunately high price of the drug prevents the determination of this question.

The first of these cases of uro-lithiasis is Miss L. F.,* aged twenty-eight, who came under observation February 12, 1891, with a history of an almost continuous ache in the right loin for seven to ten months. Paroxysms of pain at times occurred, shooting towards the bladder. She had been passing gravel more or less continuously for several years. There were anorexia, constipation, bad taste, leucorrhœa, painful menstruation, and severe headache occurring about twice weekly. She was in a melancholic condition; was persistently low-spirited, the latter, doubtless, being induced somewhat by the recent death of her favorite cousin from a somewhat similar ailment. Her urine then was noted to be highly acid, of a specific gravity of 1028, and to contain neither albumin nor sugar. Microscopically, there were numerous crystals of ammonium urate, large excess of free uric acid, and microscopic (good-sized) calculi of both ammonium urate and uric acid. There were also amorphous urates, a few pus-cells, red blood-corpuscles, and epithelium from the kidney's pelvis and from the bladder. There was then present deep-seated tenderness in both flanks, but no palpable tumor. She was placed upon large doses nightly of nascent potassium citrate, was given hot water freely before breakfast, and was directed to take liberally of an alkaline mineral water through the day, and to live in the open air.

From the date of the first visit she was under

* A cousin of the patient upon whom a nephrotomy for calculus pyelonephrosis was done by Professor Keen, and reported by us in the THERAPEUTIC GAZETTE, January 1, 1892. These two young women strikingly resembled each other in appearance, disposition and temperament.

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observation quite constantly, with the exception of an occasional interval of about two months, until piperazin was begun in January, 1892. In the early part of this period her general condition improved somewhat under remedies directed to assisting the impaired digestion and the use of arsenic after meals. The vegetable salts of potassium were given for a number of months in very full doses, intermittently. A lithia-water was also taken freely. Potash could not be continued for any length of time, from the almost invariable gastric derangement it occasioned. During this period frequent chemical and microscopic examinations of the urine were made. The result of these was similar to that above recorded. Pus- and red-cells were never present in large amount, nor could pus even be detected by Donné's test. Crystals of uric acid and urates were usually present in huge excess, and occasionally calcium oxalate abounded. Cells from the kidney pelvis were common, and on several occasions hyaline and granular casts were seen. The daily quantity of urine was subnormal,—about 1½ pints, and often but 17 to 18 ounces,—unless considerable doses of potash or large quantities of fluids were taken. The urea was always low, on several occasions averaging between 142 and 216 grains. Attacks of gravel were very frequent, but were usually dissipated by potash, to promptly return on its discontinuance, despite care in diet and attention to general hygiene. For this reason and because of the disorder of digestion full doses of the alkalies occasioned, she, after a few months, abandoned their use, and then symptoms of stone in the kidney became more pronounced. There was constant severe pain in the loin, with increased tenderness on pressure, and growing fulness, dulness, and resistance in the flank. Professor Keen at this time saw her with me, agreeing as to the probable existence of stone, and advised a nephrotomy. To this consent could not be obtained. I now lost sight of the case for several weeks. During this time she took a great deal of lithia-water, but no drugs. Early in January, 1892, when I again saw her, the symptoms were those of calculus hydronephrosis. She was passing less than 2 pints of urine daily, and often scarcely a pint. There was prominence, tenderness, and dulness in the left hypochondriac and iliac regions, the dulness extending towards and near the umbilicus, and, posteriorly, to the usual situation of the kidney. I now began a brief trial of two drugs,—diuretin and piperazin,—a barren result with which, I informed her, would necessitate immediate operative interference. Diuretin was first prescribed, principally because she was then suffering greatly from migranous headache, which, it was thought, diuretin would relieve. Little was expected from either it or piperazin on the kidney condition. About a drachm daily of the former was taken for a week or ten days, totally without effect on the urine. Piperazin was now ordered in doses of 15 grains daily. The issue of the use of this remedy seemed quite extraordinary, so promptly and decidedly did benefit accrue. The urine, which had been unaffected in amount by diuretin, after taking piperazin for three or four days, underwent a most decided increase; from but a pint daily it rapidly rose to 4 pints. When seen on February 27, 1892, she had been taking piperazin for over two weeks. There had been voided in the preceding nine hours 5 pints, a much greater quantity than she is aware of passing before or since.* The loin-pain was much diminished, and the fulness and dulness occupied a much less area. Her general condition in the two and a half weeks had also undergone a striking improvement, noticeable to all. Appetite and digestion were asserted to be better than for several years,—the bad taste to have disappeared; in short, she looked better and felt generally improved, an amelioration, doubtless, largely of psychical origin, contributed to by the feeling that her condition was no longer one of desperation. No minute examinations of urine were possible immediately preceding the administration of piperazin, her condition not admitting of delay in its use; nor was any attempted directly after she was seen on this occasion, it being intended, after the condition had ameliorated sufficiently to allow discontinuance of the drug for a time, to undertake systematic examinations. To my regret, also, it was impossible to keep a continuous record of the daily amount of urine passed from the time piperazin was first begun; this was, however, done subsequently, on starting anew with the remedy, after its temporary withdrawal. From February 12 to April 2 (the last, one of the dates of temporary discontinuance) the daily dose was from 12 to 20 grains, usually the latter. The daily quantity of urine was always fair and often large. She was careful, by direction, to take the same amount of fluid daily, averaging about 1½ pints, not including that in the food eaten. On March 10 the amount passed was 65½ fluidounces; specific gravity,

* The passage of this large amount, under the conditions narrated, can only be explained by the giving way of a hydronephrosis.

1010; faintly acid; urea, 300 grains. March 11 to 15, the amounts were 61, 70, 59½, and 70 fluidounces. March 16, 50 fluidounces, faintly acid; specific gravity, 1020; urea, 500 grains; uric acid, 17 grains.* March 17 to 23, the amounts were 62, 47, 63, 64, 62, 54 fluidounces. March 30 and 31, 51 and 53 fluidounces.

Piperazin was discontinued from April 2 to 13. During the period of seven weeks in which the drug was taken, improvement continued, though not so markedly as at first. Pain, or a sensation of soreness in the loin, persisted; much slighter, however, than formerly, and little tenderness was induced by pressure over the area of fulness and dulness in the lumbar region. This last was now present in moderate degree only.

The subjoined table gives the consecutive daily specific gravity and quantity of urine, and also the variations in its most important nitrogenous constituents, estimated from mixed twenty-four-hour specimens, prior to and following the administration of piperazin.

In all estimations in this paper the acidity, urea, and uric acid were obtained by the following methods: The acidity was estimated by titration with a $\frac{N}{10}$ solution of NaHO; titrations were made as early as possible after receiving the specimens, which were usually sent promptly after mixing at the expiration of each twenty-four hours. Urea was estimated by the hypobromite process (bromine itself being always used), with the apparatus of Parke, Davis & Co. Uric acid was estimated by the now well-known and reliable method of Haycraft; as with the urea estimations, a second of uric acid was often made to confirm the first.†

Microscopic examinations were made between April 8 and May 9. In all specimens there were an abundance of amorphous urates, free uric acid and ammonium urate crystals, large

CASE I.—MISS L. F.

Date.	Daily amount of urine in fluidounces.	Specific gravity of mixed 24-hour specimen.	Degree of acidity calculated on 100 c.c. of urine.	Daily elimination of urea in grains.	Daily elimination of uric acid in grains.	Daily dose of piperazin.
April 8.	47	1016	22	307	13	None for 6 days.
April 9.	50	1015	20	300	11½	None for 7 days.
April 11.	58	1016	28	450	15	None for 9 days.
April 12.	42½	1010	15	250	8	None for 10 days.
April 13.	52	1013	18	331	12	None for 11 days.
April 14.	63	.....	...	.....	...	18 grains of piperazin daily.
April 15.	75	.....	...	.....	...	18 grains of piperazin daily.
April 16.	62	.....	...	.....	...	18 grains of piperazin daily. Through a misunderstanding specimens were not sent on the 14th, 15th, and 16th, so that no estimations could be made. Piperazin was, therefore, stopped until April 28, that consecutive daily examinations might be again made immediately before taking and while on the drug.
April 24.	50	1013	12	273	15⅜	No piperazin for 7 days.
April 25.	51	1015	20	273	14⅜	No piperazin for 8 days.
April 26.	46½	1011	30	245	11⅛	No piperazin for 9 days.
April 27.	56	1012	24	316	15⅜	No piperazin for 10 days.
April 28.	43½	1020	30	496	15⅜	No piperazin for 11 days.
April 29.	60	1012	14	330	14⅜	18 grains piperazin taken.
April 30.	55	1012	12	420	13¾	23 grains piperazin taken.
May 1.	50	1020	20	386	15⅜	33 grains piperazin taken.
May 2.	55	1012	20	423	13¾	33 grains piperazin taken.
May 3.	44	.....	...	.....	...	23 grains piperazin taken. Specimen of urine not received.
May 5.	60	1012	10	440	19⅘	23 grains piperazin taken.
May 6.	44	1020	10	400	20	23 grains piperazin taken.
May 7.	53	1016	22	390	11¾	20 grains piperazin taken.
May 8.	51	1019	30	280	19	20 grains piperazin taken.
May 9.	47	1013	20	342	14½	20 grains piperazin taken.

* Within these dates other urea examinations were made, but as the urine was partly decomposed, the results were considered untrustworthy, so are not here recorded. A number of other uric acid estimations were also made, but by a method the technique of which was afterwards proved faulty, so that no account is here taken of these.

† No account of the daily elimination of urinary solids is here appended, as these may be readily approximately estimated by multiplying the last two figures of the specific gravity of the urine by 2.33 (Christison's formula), or by 2 (that of Trapp's). This equals the percentage in grammes calculated on 1000 cubic centimetres.

quantity of granular *débris*, and epithelium from the kidney and bladder.

The urine was not examined from this on. An estimation of the amount passed in the twenty-four hours, however, was still frequently made. From May 12 to 24 the daily quantities were in fluidounces 47, 44, 36½, 55½, 49½, 56½, 44, 43, 42, 48, 53, 50, 50. During the second half of June and the early part of July similar counts were made, which it is needless to reproduce here, since they deviated very little from the foregoing, like them being quite normal.

Piperazin was continued in daily quantities of 20 grains until August 1. It was then withheld, it being concluded that the patient had entirely recovered. Four weeks succeeding its discontinuance the urine was measured for four consecutive days. The amounts were, in fluidounces, 50, 52, 48, 47. All loin-pain and discomfort to manipulation in the renal region had completely disappeared when the patient was examined on June 3, and had not since reappeared when last seen, on October 1, 1892, though she was leading a most sedentary life and taking little or no exercise in the open air. When the abdomen was last thoroughly examined, in June, resistance and dulness were still present in a limited portion of the situation previously occupied by the hydronephrosis, but no tenderness, even on deep pressure, could be elicited in this region. No gravel has been noticed in the urine at any time from the date of commencement of piperazin, though looked for by the patient. Prior to taking piperazin, the freshly-voided urine almost constantly contained it, but in less amount than when the patient first came under observation. No untoward results occurred from the long-continued employment of piperazin. Menstruation during several monthly periods was profuse, and more frequent than had been customary. What effect piperazin had in the production of this, I do not know. Appetite and digestion seemed to be better while piperazin was taken. Headache, from which she has always been a sufferer,—probably largely due to eye-strain,—continues as before.

The second case is one of striking interest, because of the long-continuance of symptoms of stone in the kidney, and the fact that lack of certain common indications of that affection, and that of an accompanying pronounced pyelitis, prevented its recognition by a considerable number of practitioners consulted at various times.

The patient came under observation accidentally. My attention was incidentally called to him as he lay in a paroxysm of colic, in the out-patient ward of the Jefferson Hospital. It appeared that he had been in the habit for some time of going to the resident about twice weekly for hypodermic injections of morphine, because of recurring attacks of severe pain in the right lumbar region, which came on suddenly, incapacitating him for work, and which were ultimately relieved by rest and full doses of morphine. At first I was inclined to the opinion that the man was a malingerer; but a careful inquiry into his history, and an examination of the urine, which I had him send me on the day in which I first saw him, caused me to take a different view of his complaint. The following are the chief points in the case:

A. L., aged thirty-eight; clerk. First seen December 14, 1891. For seven years he had had, at intervals of four days to two weeks, attacks of severe pain in the right loin, occurring suddenly, and lasting from twelve hours to one or two days. Occasionally an attack would continue for almost a week, during which pain never would be absent, though not constantly severe. The initial attack occurred while serving as a United States army private. He was then on the plains, engaged in digging holes for the erection of telegraph-poles. The pain was always deep-seated in the loin. He could not recall it ever shooting towards the bladder or into the testicle, nor was frequent urination a symptom. During and especially succeeding the attacks he had noticed, particularly in the past year or so, that the urine was of an unnatural dark-red hue. This he had not recognized as blood, though it undoubtedly was. Vomiting was not an infrequent concomitant of severe attacks. No access of pain could be elicited by manipulation in the renal region during the attacks. There was absolute freedom from pain in the intervals, and repeated examinations of the abdomen revealed no abnormity of any of the viscera.

He was a robust fellow, with good general health apart from these attacks. The habits were temperate. Gravel had never been noticed in his urine, though it might have been present preceding the appearance of the trouble, or even succeeding its onset, as it had not been looked for. He had consulted a number of physicians, who had treated him principally for gastric and intestinal indigestion. One or two had suggested nephralgia. The operation of stretching the ilio-hypogastric and ilio-inguinal nerves had been undertaken by a surgeon a year or so before with a view of

thus relieving the attacks. Stone was not then suspected, it being asserted that, were it present, the symptoms suggested a new phase of that affection. It is said that the kidney was felt during the operation, and no stone detected. Despite this testimony, I believed the case in all probability one of renal calculus, and an examination of the urine during and following an attack strengthened this opinion. It was of very high color, and, after a day's standing, deposited a dark-red sediment to the extent of one-half the bottle in which it was contained. Microscopically the sediment consisted entirely of blood-corpuscles and pus-cells. Portions taken from the upper layer had the appearance of a drop of leucocytic blood. The lowest stratum consisted almost entirely of pus-corpuscles. A specimen voided two days after the attack was acid, of light amber color, specific gravity 1020, and contained $\frac{1}{15}$ per cent. of albumin (Esbach's method). After some hours' standing, a sediment was precipitated, which, microscopically, consisted solely of pus-cells, containing entangled calcium oxalate and uric acid crystals, the last in less amount than the lime oxalate. Sufficient pus was present on decanting the urine to gelatinize the deposit with liquor potassæ, a response always obtained when this test was similarly applied to a number of subsequent specimens.

I represented to the patient that he had beyond doubt a suppurating kidney, which was in all probability due to a stone lodged therein, earnestly advising him to submit to a second operation. But to this advice he would not listen because of his previous experience in this direction.

Because of its unusual interest, the case was kept under observation that a more extended study of his condition and that of the urine could be made. It was thought that he would

CASE II.—A. L.

Date.	Daily amount of urine in fluidounces.	Specific gravity of mixed 24-hour specimen.	Degree of acidity calculated on 100 c.c. of urine.	Daily elimination of urea in grains.	Daily elimination of uric acid in grains.	Daily dose of piperazin.	Remarks
April 15.	28	.....	...	.....	...	None taken for 8 days.	Just recovering from an attack; urine dark red; contains much blood, pus, and amorphous urates.
April 16.	32	1027	42	436	20	None taken for 9 days.	Color high; turbid; no blood macroscopically; few red disks microscopically; pus-cells in large number.
April 17.	49	1022	22	378	Not estimated.	None taken for 10 days.	
April 18.	68	1021	13	518	Not estimated.	None taken for 11 days.	
April 19.	52	.....	...	....A	Not estimated.	None taken for 12 days.	
April 20.	62	.....	...	.....	Not estimated.	None taken for 14 days.	
April 22.	49	1020	44	423	26	None taken for 15 days.	Slight attack.
April 23.	42	1022	48	462	25	None taken for 16 days.	
April 24.	48	1020	30	433	18	None taken for 17 days.	
April 25.	70	1021	18	509	14	None taken for 18 days.	
April 26.	50	1016	16	432	15	25 grains taken.	
April 27.	58	1021	36	493	24½	30 grains taken.	
April 28.	44	1022	40	500	18½	30 grains taken.	
April 29.	34	1022	70	382	13	30 grains taken.	Urine contains blood; slight attack; ¼ grain morphine taken.
April 30.	37	1022	38	420	15	20 grains taken.	Microscopic examination of urine, pus-, and red-cells; urine still bloody.
May 1.	84	1020	20	611	22	20 grains taken.	Attack ceased April 30; urine light color; turbid.
May 2.	76	1020	13	518	26	20 grains taken.	
May 3.	48	.....	...	.....	...	30 grains taken.	
May 4.	48	.....	...	.....	...	30 grains taken.	
May 5.	41	1024	48	503	18	30 grains taken.	
May 6.	43½	1027	48	579	21	30 grains taken.	Pus-corpuscles; renal epithelium, bacteria; uric acid and urates.
May 7.	36	1016	52	475	19½	30 grains taken.	Attack coming on.
May 8.	23	.....	...	.....	.....	30 grains taken.	Preceding this table a report of the microscopic examination of this specimen is given.

ultimately submit to an exploratory nephrotomy, and that thus the diagnosis could be confirmed. Little was expected from a resort to drugs because of the pronounced pyelitis complicating the condition.

I made in all thirty-two chemical and eighteen microscopic examinations of the urine. On a number of occasions two or three specimens passed at the time of an attack, at its onset, height, and termination, were examined microscopically. Pus was always present in some amount, except on a single occasion. Blood also could be noted always macroscopically and microscopically at the end of an attack, and frequently microscopically at its height; never, however, several days after its entire cessation. Epithelium from the kidney pelvis was frequently found, and on three occasions hyaline and epithelial casts were noticed. The urine was always acid when freshly voided; it usually was quite fetid, the latter especially after standing a short time. The mixed twenty-four-hour specimens were turbid, and could not be cleared by heat and filtration. Calcium oxalate crystals were nearly always present in large amount, but occasionally uric acid and urates were in preponderance. Albumin constantly existed in small amount, $\frac{1}{10}$ to $\frac{1}{20}$ per cent., evidently of pyuric origin.

On several occasions the quantity of urine passed during an attack was diminished, though it was normal in amount at the termination, leading to the supposition that the ureter of the affected kidney might be temporarily closed.

On May 8, in a mixed specimen of the total twenty-four-hour urine (23 fluidounces), passed at the height of an attack, there was, in three slides examined, but one pus-corpuscle seen in one slide, three in a second slide, and none in a third, with no blood disks. There were amorphous urates and uric acid crystals. The examined portion was taken from different layers of the sediment, which, in this single specimen, was evidently due to amorphous urates and not to pus. This would indicate temporary obstruction of the ureter of the diseased kidney during this attack; for, also, immediately following it (May 9) blood and pus were present in some quantity. A daily estimate of the amount of urine passed was made, by my direction, for several months. But symptoms of closure of the ureter occurred with no frequency or constancy of relation to the paroxysms. Often, too, when a diminution in quantity of urine took place, it continued until several days after pain had ceased, with no very decided increase in amount subsequently, to indicate cessation of a hydronephrosis.* During the last of January large doses of potassium citrate were prescribed; this salt was continued for one month. Prior to and during this time frequent examinations for uric acid and urea were made. The result of these need not be recorded here. The urea, when potash was not administered, was usually somewhat diminished, varying between 350 and 465 grains daily, and occasionally sinking to below 300 grains. The daily elimination of uric acid was usually in excess. While taking the potassium an increase in the amount of urea and a diminution in uric acid occurred, as is usual.

Piperazin was begun on March 27, 1892, and continued steadily until July, with a single interval of eighteen days. In this time he took thirty 5-gramme bottles, in daily doses varying from 12 to 30 grains. Daily quantitative examinations of the urine as to acidity, uric acid, and urea were made preceding taking the piperazin and immediately succeeding its beginning. This was done in two periods. The second is given in the subjoined table (page 25), as the dose resorted to at first was thought to be too small to materially influence the urinary secretion. Little difference, however, actually exists as to quantity or quality of urine voided at these times under piperazin.

Estimations were now no longer made. Continued daily measurements for some time of the amount of urine passed tallied closely with the foregoing. The attacks became less frequent and severe until the ensuing (last) July, when the more violent ones ceased to occur. The patient was not seen for several months until summoned December 1 for report, prior to preparing this paper. He stated then he had noticed no blood or pus in the urine since early in June, and that none of his former attacks had recurred. At intervals, varying from a month to six weeks, he feels for two or three days a sensation of discomfort not amounting to actual pain in the loin. This always disappears without his having recourse to medicine. This same discomfort he had when I saw him. A specimen of urine was then voided, and examined after standing twenty-four hours in a conical glass. It had remained clear; was of light amber color; non-fetid; specific gravity, 1020; contained no albumin by heat or nitric acid† (including overlaying a cold specimen of

* Infrequently the urine increased considerably in amount during an attack. Thus, in one twenty-four hours, 85½ fluidounces were passed. On this occasion no solids were eaten, and four quarts of milk were taken.

† It was possible always to demonstrate albumin by these coarser tests in the previous specimens.

it with the latter), but responded slightly to the ring-test with citrated picric acid. The sediment was flocculent and very small in amount. A number of fields in three slides were examined. Pus-corpuscles were present in small amount. Many fields contained none. One field held eight to ten bunched. Three round cells, apparently from the kidney, were present. One large hyaline and a number of casts of urates were seen; urates and uric acid crystals were numerous.

The third case is in all likelihood one of mulberry calculus.

Miss A. A., first seen August 16, 1891. For four years there had been present stationary pain in the right lumbar region, occasionally accompanied by slight paroxysms, in which the pain darted in the direction of the ureter.

CASE III.—MISS A. A.

Date.	Daily amount of urine in fluidounces.	Specific gravity of mixed 24-hour specimen.	Degree of acidity calculated in 100 c.c. of urine.	Daily elimination of urea in grains.	Daily elimination of uric acid in grains.	Daily dose of piperazin.
April 9.	30	1033	50	400	15⅔	6 days after discontinuance of a daily dose of 9 grains.
April 10.	28	1033	46	446	15	No piperazin.
April 11.	32	1034	43	349	19⅓	No piperazin.
April 12.	27	1030	42	321	14⅛	24 grains taken.
April 13.	30	1033	44	368	20	24 grains taken.
April 14.	32	1026	34	381	15	24 grains taken.
April 15.	40	1023	28	346	15	24 grains taken.
April 16.	48	1025	33	414	8	20 grains taken.
April 17.	34	1032	54	454	15	22 grains taken.
April 18.	27	1027	38	212	7½	22 grains taken.
April 19.	32	1032	31	398	18	22 grains taken.
April 20.	32	1031	46	480	15	22 grains taken.
April 21.	36	1025	40	408	15	22 grains taken.
May 4.	30	1030	52	340	14	20 grains daily up to May 2; then 30 grains daily to date.
May 5.	30	1030	52	400	15	30 grains.
May 6.	32	1032	47	350	13⅓	30 grains.
May 7.	37	1022	42	385	12¾	30 grains.

The pain was present intermittently at first, but had been constant in the past year. About the time this trouble began she had two quite characteristic attacks of renal colic, lasting each a day, and accompanied by bloody urine. She does not know if she then or since passed a stone or gravel. On examination, there was noted an extended area of renal dulness on the right, with decided tenderness on pressure over it. The left loin was normal. There was a systolic apical heart murmur, due to mitral incompetency, probably the result of a past attack of endocarditis during rheumatic fever, which had occurred two years before. The urine was clear, specific gravity 1023, and contained a trace of albumin by overlaying it with nitric acid.* It was loaded with calcium oxalate, and microscopic calculi of the same. There were a few pus-corpuscles, red blood-disks, epithelium from the kidney and bladder. Several other specimens were examined microscopically within a short time. Calcium oxalate crystals were always present in large amount, with a few blood- and pus-corpuscles.†

I concluded the calculus to be of calcium oxalate formation, and therefore scarcely susceptible of solution. I, however, thought it wise to make a thorough trial of a vegetable salt of potassium, as there was, of course, a possibility of the stone being composed of uric acid or urates. Potassium citrate was administered in very full doses for six weeks, totally without result. At the expiration of that time absosolutely no improvement resulting, I had Professor Keen see her, with a view to operation. Professor Keen agreed as to the diagnosis, and advised an early exploratory operation. But to this her consent could not be obtained.

Piperazin was begun in March, 1892. At first it was taken in doses of 9 grains daily, and later in much larger quantities. It was

* Albumin was examined for a number of times. It was inconstantly present to Heller's test, but always responded to picric acid.

† A number of subsequent examinations were made. They all agreed substantially with the above, save that hyaline casts were found several times, and once granular casts, and that, after taking piperazin a week or ten days, calcium oxalate crystals were present in very much less amount.

continued until July. Prior to beginning piperazin the amount of urine passed was always subnormal. The gravity was usually high (1030 or over). The daily amount of urea was about 400 grains. It will be seen by the accompanying table that the quantity passed was uninfluenced, and continued small as before. The diminished amount constantly passed may in a measure be accounted for by the fact that the patient habitually partook most sparingly of fluids.

A number of urine examinations were made before taking piperazin and while on the drug. A second series is given in this case, as in that of the case preceding, because the dose first resorted to—9 grains daily—was thought too small to materially influence the amount or quality of the urine. The first series, however, agrees substantially with that of the second.

Piperazin in this case, as regards effects on the symptoms, loin-pain, etc., was most disappointing. No substantial benefit can be said to have resulted from its trial. At first it was thought improvement was occurring. The loin-pain diminished and less tenderness existed to pressure. This amelioration, however, was not maintained; and now, as regards the kidney derangement, she is apparently in the condition she was prior to instituting the piperazin treatment. The loin is as tender, the aching as severe, and occasionally darting pains occur from the kidney into the hypogastrium.*

In the first and second of these cases practically a cure may be said to have been obtained. Undoubtedly a cure has resulted in Case I., as all symptoms referable to the kidney have been absent several months, notwithstanding piperazin was discontinued six months ago. A most interesting fact in this case is the permanent disappearance of gravel from the urine. Gravel had been a persistent and troublesome symptom for months prior to treatment with piperazin. In the second case, one of undoubted pyelitis, in all probability calculus (uric acid or calcium oxalate), the pus has almost entirely disappeared from the urine. It now manifests its presence only by microscopic examination. None of the former attacks of lumbar pain, of seven years' continuance, have been present for seven months.

In the third case—that of probable mulberry calculus—no benefit has been obtained by the use of piperazin. This is in accordance with what might be anticipated from the behavior of piperazin to this salt of calcium, upon which it has no solvent action.

* These were occasionally present when she first presented herself for treatment. They became a trifle more common after piperazin was begun.

What is the action of piperazin in cases of nephrolithiasis in which a cure is obtained? The answer seems not far to seek,—by its marked disintegrating effect upon uratic stones lodged in the kidney pelvis, which it bathes in process of elimination. In the test-tube the solvent action of even dilute (one per cent.) solutions of piperazin upon portions of uratic calculi is decided. In a warm chamber, with an equable blood-heat temperature, these are readily softened in a few hours, and this effect is more decided if the solution is permitted to flow slowly over the stone. But if calculi are so dissolved in the kidney, an increase in the uric acid eliminated is to be expected during their disintegration, if a stone of large size is in question.† This increase, though carefully examined for, was not detected in my cases. It may be that it occurred in Case I., as estimations could not be undertaken for several weeks after piperazin was begun. Then great improvement in symptoms had occurred. In the second case the doses first used were too minute for this result to be anticipated. The symptoms continuing, the remedy was withdrawn, estimations were made, and larger doses administered. However, no increase in uric acid attributable to the remedy was evident. But also no marked diminution in symptoms of stone occurred while estimations were in process. Distinct amelioration did occur later, while the remedy was being taken in full doses, but when the case ceased to be under continuous observation. In this case the stone, perhaps, being a mixed one of calcium oxalate and uric acid, was more difficult of solution, so that disintegration occurred too gradually to produce early appreciable results.

Our present knowledge of the precise mode of action of piperazin is so limited that little more than theorizing as to the cause of the results obtained can be attempted. That piperazin is beneficial in cases of gravel and stone is certain. Sufficient clinical reports are now on record as to this. Its precise mode of action is still somewhat obscure, and has not been determined by those hitherto investigating the subject, judging from the contradictory statements, all of which are based on narrowed data. Ebstein and Sprague‡ found no alteration in urea

† It should, however, be here stated that a uric acid calculus may be of some size—that of a pea or larger—and yet weigh but a grain or two. Such a stone, requiring several days to disintegrate, would not appreciably affect the amount of uric acid excreted. A very large calculus would, of course, weigh much more; evidence of its prompt solution should then be apparent.

‡ *Berl. Klin. Woch.*, No. 14, 1891.

or uric acid excretion, but noted an increase in the amount of urine, which, at times, became of an alkaline reaction. Bardet* reported an increase in the soluble urates, while Vogt's experiments showed a diminution in the latter, with an increase in urea. Brik† more recently records Heubach and Kuh's having detected a slight increase in excretion of uric acid, while he himself noted an increase in quantity of urine; but, as with Heubach and Kuh, Brik found no alteration in the reaction, it never becoming alkaline during administration of piperazin.

Extended examinations as to the effect of piperazin on nitrogenous excretion in the urine should be made in both healthy and uratic subjects before accurate judgment can be arrived at as to mode of action. This I had myself undertaken, but was temporarily forced to abandon because of pressure of other work. Uric acid estimations by trustworthy methods are troublesome and consume much time.

In cases of uric acid diathesis other than stone, from what is known of the solvent effects of piperazin on uric acid and the solubility of piperazin urate, an increase in excretion of uric acid might be expected under full doses of piperazin. Yet some observers have reported a diminution, with a corresponding increase in urea, indicating that, besides its affinity for uric acid, piperazin promotes the transformation of uric acid into urea, as do markedly the salts of potassium with the vegetable and carbonic acids. These potassium salts were long ago asserted by Basham to act by virtue of the increased alkalinity of the blood they produce, promoting its oxidation function, and this explanation is now generally accepted. When these salts of potassium are administered, the acidity of the urine is promptly diminished, and soon disappears, while the quantity of uric acid is reduced to a minimum, and that of urea increased often several fold. Piperazin has been asserted to produce identical results on the reaction of the urine, and to also markedly augment urea elimination. I am, however, unaware of any authentic instance of the urine becoming alkaline after the use of piperazin. Perhaps larger doses than those usually administered would induce this; ½ drachm daily for some days in several of my cases failed to effect this. It may be seen by the foregoing tables that the acidity quantitatively estimated from mixed twenty-four-hour specimens was not appreciably affected by the drug. Nor can it be said that an increase in urea excretion occurred in my three cases, judging from the estimations made immediately before and after giving piperazin. In Case I., during the first five days on piperazin, in which 135 grains were taken, subsequent to its temporary discontinuance there were only 1989 grains of urea excreted against 1603 in the five days preceding, a total increase of but 395 grains. A total increase of 14 fluidounces of urine also occurred. In Case II., 2259 grains of urea were eliminated in the first five days, and 2406 in the second, in which 135 grains of piperazin were taken, a total increase here of but 147 grains. A total diminution in urine occurred in the second five days of 2 fluidounces. In Case III., 1195 grains of urea were passed in the first three days, and 1070 in the second three days (when on piperazin in doses of 24 grains daily), a total diminution in urea of 125 grains. A total diminution in urine also occurred in the second three days of 2 fluidounces. These differences in urea excretion are, of course, too slight and common to be attributed to the administration of piperazin.‡ The extraordinary increase in urine in Case I. under piperazin, and the subsequent maintenance of the normal average, is explicable on the probable supposition I have already advanced,—that of the removal of a hydronephrosis by rendering patent a ureter occluded by stone. In the other two cases no increase in urine occurred, which somewhat surprised me, as in several other instances in which I administered piperazin a more or less marked increase is stated to have occurred under it, though no measurements were made.

* *Bull. Gèn. de Thèrap.*, March 8, 1891.

† *Wien. Med. Blätter*, December 10, 1891 (see THERAPEUTIC GAZETTE, p. 113, February, 1892). Heubach and Kuh's paper appeared in *Internat. Centralb. f. d. Physiol. u. Pathol. der Harn u. Sexualorgane.* See "Notes on New Remedies," December, 1891. Abstracts of most of the recent literature on piperazin will be found in late issues of the last-named journal.

‡ In two similar periods of five consecutive days, when on no drug, a difference in the amount of urea excreted in my own urine amounted to 250 grains.

PIPERAZIN.—Drs. BIESENTHAL and SCHMIDT review (from the *Berliner Klinische Wochenschrift* in *Therapeutic Gazette*) the clinical reports on piperazin which have appeared recently. The reports of VOGT, EBSTEIN, HEUBACH, KRAKAUER and BRIK, all based on the use of Schering's Piperazin, are all very favorable. Testimony seems to be nearly unanimous that the remedy is harmless, and that it is effective as a solvent of uric acid. BIESENTHAL and SCHMIDT report seven cases in which the remedy has been tried. Four of the cases are given in detail. In three of the latter, who were gouty patients, and had attacks of gout, marked relief was obtained. The fourth patient had violent attacks of renal colic. On the first day the piperazin was used an extraordinary quantity of gravel was passed. After the second dose, on the next day, large quantities of gravel were passed several times, and almost immediate relief was experienced. Similar results were obtained in other cases. BIESENTHAL and SCHMIDT recommend the remedy very highly. Internally, they say, piperazin is best given in dilute solution in doses of fifteen grains distributed during the day. Its taste is very slight. As it is not irritating to mucous membranes, a one or two per cent. solution may be employed in washing out the bladder in the case of vesical calculi. Hypodermic injections into gouty deposits and local applications to gouty swellings may also be employed.

About two years ago the Chemische Fabrik auf Actien, vormals E. Schering, of Berlin, after long experimenting in its laboratory by its staff of chemists, produced a new chemical product, which at first seemed to be identical with spermine. Through clinical trials this supposition was quickly found to be erroneous, but further experiments developed the interesting fact that the new product was a uric acid solvent. This notable scientific discovery was achieved independently by the Schering laboratory, and it deserves credit for enriching materia medica with so valuable a new therapeutic agent.

The name "Piperazin" was adopted for the product, and Piperazin-Schering has in two years become widely known to the medical profession throughout the world, as the most powerful uric acid solvent known. Scores of clinical reports by the highest authorities, among them such names as Bardet, Biesenthal, von Mering, Schwenninger, Vogt, Ebstein, D. D. Stewart and J. H. Bradford (the last two of Philadelphia), have been published in the leading medical journals of the world; and all these reports were based solely on the use of Piperazin-Schering.

Now, recently, a German manufacturing firm which furnishes a number of other new remedies, has claimed to have discovered a new process yielding a product which they claim is identical with Piperazin-Schering; and without waiting to give their product thorough clinical trial they and their agents are making the attempt to sell the untried product. With reprehensible, not to use a severer characterization, enterprise they appropriated all the literature based on Schering's Piperazin for their own advertising purposes, and with other questionable methods, such as tempting by lower price, they bolster up their claims and bid for preference for their product.

It is possible that the new competing product may justify its makers claim, but is it fair to precipitate an untried remedy on the medical profession on a mere theoretical claim of identity with Piperazin-Schering. Aside from the fact that this firm has no moral right to appropriate for its own profit the legitimate property of the Schering laboratory, it exhibits superlative presumption in inviting the medical profession to use a product with which not a single clinical trial has been made or published as yet.

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