AN EFFECTIVE TREATMENT OF VESICAL HÆMORRHAGE WHEN CAUSED BY PAPILLOMATOUS GROWTHS.

By HERBERT T. HERRING, M.B., B.S.

NUMEROUS cases were formerly met with in practice of severe and persistent hæmaturia, which gradually increased, and at length ended fatally through extreme loss of blood. The cause was usually regarded during life as a renal one. *Post-mortem* examination, however, often revealed growth of flocculent matter involving sometimes large tracts of the vesical surface, sometimes single growths with either wide base or a single pedicle. Finding a marked example of the last-named by necropsy one day, my friend Sir Henry Thompson resolved that in the next case with these symptoms well marked he would make an exploratory incision on a grooved staff into the membranous part of the urethra, sufficient to admit his finger to enter the bladder, and if he found a pedunculated growth would enlarge the opening a little and remove it. An opportunity occurred in November, 1880. He carried out the plan literally, and curiously enough found a typical specimen of pedunculated growth, which he removed without any difficulty. The man recovered quickly, had no recurrence, and was living and well ten years later.

After many subsequent similar operations, Sir Henry Thompson found that the broad-based tumours and the multiple growths formed the larger proportion of these cases, rendering nothing short of a suprapubic operation feasible, and then by no means always adequate to the removal of the growth. It thus occurred to him to try the effect of continued and frequent injections of nitrate of silver to repress or destroy the growth, and he met with two or three notable successes. These I conducted for him, and have since carried out in my own practice at his special request, with a result which enables me to say that we have found for most if not for all of these cases a real cure—at least a powerful agent for checking the increase of the growth.

The diagnosis of every case here recorded has been verified by removing a portion of tumour and subjecting it while quite fresh, without staining or hardening, to microscopic examination. Such specimens may be usually obtained by washing out the bladder freely with warm sterile water, examining the *débris* brought away for shreds of tissue and mounting them at once for microscopic investigation. Unless this is done immediately, typical specimens are not easy to find; they readily break up and decompose if left to macerate.¹ No case has been accepted without this test.

The instruments used are a No. 7, soft, polished, slightly *coudée* catheter with the eye situated near the end, and a 4-oz. india rubber bottle furnished with a brass taper nozzle and stopcock, together with a standard solution of 1 gr. of nitrate of silver to 1 drachm of distilled water, acidulated with a small quantity of free nitric acid.

The injections have been commenced by adding half a drachm of the standard solution (that is, half a grain of the nitrate) to four ounces of warm water (99° F.), and the strength gradually increased every day or two until one, or even sometimes two drachms, has been added. The maximum strength varies very much in individuals. I have never found it exceed two drachms, and it very often falls far short; but it is of the greatest importance so to regulate the strength of the nitrate of silver that no pain, increased frequency of micturition, or straining should follow the injection; and the only knowledge the patient may have of the operation is a certain feeling of warmth in the region of the bladder, which should entirely subside within half an hour. By thus very gradually increasing the quantity of nitrate of silver, the bladder becomes more tolerant, and a stronger solution can be injected without producing any of the above-mentioned symptoms than would be possible if the full dose were resorted to at once. Occasionally, when the maximum strength has been in daily use for a considerable period, the bladder becomes irritable and the strength must be reduced, but the treatment should not be stopped.

As soon as the patient has learned to inject himself efficiently—throwing into the bladder half the contents of the

bottle, retaining the solution for a few seconds and then letting it run off, and repeating the same process with the second half—he should do so daily; at night, perhaps, is the best time, for it is always advisable to rest afterwards. Before a patient can be trusted to make the injection himself, it is necessary to give him a few lessons in a uniform and systematic way of doing it, so as to ensure perfect aseptic conditions, absence of injury or irritation to the organs, and the desired effect of the nitrate in the bladder. He should continue this without intermission for four, five, or six months, reaching his maximum strength of solution some five, six, or more weeks from the commencement of the treatment. If then bleeding has ceased, as it should have done, he may inject every other day for six months longer, and afterwards every third day for a variable period. A patient having been subjected to this long course of treatment may discontinue the application, even for a year, without any symptoms recurring; but he should return to daily injections—commencing with the minimum strength and gradually increasing—immediately blood reappears in the urine. In this way hæmaturia, and also the growth, may be permanently controlled, and the patient may live in comfort for many years (Cases II, III, V, VI, VII).

The treatment at the start may occasionally increase the hæmorrhage, but after several applications the blood lessens in quantity and finally disappears (Cases I, II, III, IX, XII). In a few cases it never entirely ceases throughout the treatment (Cases VIII, IX), and is especially noticeable in small quantities at the time of catheterisation, though every precaution may have been taken to introduce the instrument with care. It is apparently caused by the catheter damaging a growth situated near the neck of the bladder. In such a case, when the treatment is discontinued the hæmorrhage ceases and the after-effect may be quite satisfactory.

Antiseptic precautions are, of course, of the utmost importance. The catheter should be well washed with soap and water, rinsed and plunged into water at 150° F.² To lubricate the instrument I prefer plain olive oil or "liquid paraffin," which has been previously heated in small quantity in a test tube to 212° F. or more. The latter is perhaps the better as it is not easily decomposed by heat, and is an excellent lubricant. Carbolic oil, so generally used, is not antiseptic, unless in very strong solutions and freshly prepared, and is always liable to cause irritation, for it parts with its carbolic acid in the presence of moisture forming an aqueous solution. I never allow the patient to smear the oil over the instrument with his fingers, but tell him after thoroughly washing his hand to dip the catheter into the oil and then, by holding the point up, allow the oil to run over it. The end of the penis should be well cleansed with a plug of moist antiseptic wool before commencing.

It should never be forgotten that septic cystitis in a patient with papilloma of the bladder is an unfortunate complication (Cases I, VI, VIII, IX, XI). It gives rise to considerable pain, and generally increases the hæmorrhage by disturbing the bladder. The deposit of earthy phosphates on the tumour may then occasionally follow and add greatly to the patient's distress (Cases I, VI, VIII).

During the treatment shreds of tumour may often be found in the urine, differing very much from the characteristic papilloma. To the unaided eye the firm pinkish, semi-transparent tissue, composed of numerous rounded villi, has given place to a soft, white, opaque, and irregular mass. Microscopically the distinct villi, composed of easily distinguished translucent cells, arranged in irregular layers around central blood vessels filled with corpuscles, have disappeared, and it is difficult to make out either villi or cells; the cell substance is cloudy and granular, and the blood vessels have shrunk, effects produced, doubtless, by the continued local applications.

With the exception of Case VIII, in which Dr. Blackmore, of Salisbury, tried a solution of sulphur of copper (10 grs. to the ounce), no other agent than Ag NO₃ has been tried, though possibly others may be efficacious. I would also suggest that the treatment by continuous injections should be adopted after cutting, or when large portions of the tumour have been removed piecemeal through the urethra by instrumentation.

The best results from this treatment have been obtained in those cases which have remained free from cystitis when the treatment has been persevered with continuously for many months, and where the papilloma has been detected early, and the tumour composed to a large extent of papillomatous tissue. Sessile papilloma with thickened base, which gradually invade the bladder walls, are not apparently so satisfactorily dealt with, for though the bleeding may be checked by the applications the growth is not so thoroughly controlled (Nos. VIII, XI).

CASE I.

1891, January 23rd.—I saw this patient (aged 73) with Sir Henry Thompson, meeting Dr. Norris Wolfenden, each of us identifying a typical specimen of papilloma under the microscope. He was a heavy man, and complained of frequency of micturition, which had troubled him for some few weeks, and blood in the urine on several occasions after driving; but he experienced no pain of any kind. The urine was clear and healthy. After a short time he was taught to inject himself, commencing with the weak solution named, gradually increasing to 1 grain to the bottle of 4 ounces. At the commencement the bleeding was rather increased, but it gradually subsided after a week's treatment.

1892, November 16th.—He had followed the instructions suggested, having injected himself every day until March 20th, 1891, every other day until June 18th, 1891, and since then every third day. Blood seen to-day on one occasion, after an interval of twenty-one months. All other urinary symptoms have long subsided. The injections of 1 grain daily were to be resumed.

1893, June 25th.—The patient had been free from all symptoms for eight months, but has an acute attack of septic cystitis, with the usual increase of hæmorrhage. He was advised to rest and persevere with daily injections.

1893, August 10th.—The hæmorrhage had passed off under treatment by the end of June; but the urine was still cloudy and offensive. As the injection of 1 gr. caused pain, the strength was reduced to $\frac{1}{2}$ gr. once a day.

1893, September 3rd.—Ten days after the last report he was laid up with a cold. Severe throat symptoms followed, which rendered him very weak, and he died of cardiac failure on September 3rd. All local treatment during this illness had been suspended, and the hæmaturia towards the end of the time had become almost constant, though not severe.

CASE II.

1891, June 23rd.—I saw this gentleman, aged 43, with Sir Henry Thompson. He had been sent to London by Dr. Duan of Costa Rica for operation, as he had diagnosed papilloma. The patient first noticed blood in October, 1890, again in the following month, and more frequently in February, 1891, when hæmorrhage was severe, and from that date it had been more or less continuous. He had no other symptoms. A specimen of papilloma was washed out and microscoped. He commenced to inject with half a grain, gradually advancing day by day till $\frac{1}{2}$ grain was used.

1894, June 28th.—He had made daily injections, using $\frac{1}{2}$ grain without intermission from the last date until May 13th, 1893, and for the following four months every other day, when he discontinued treatment. For the first few days of the course blood was seen frequently, but it gradually decreased, and disappeared after ten days. During the whole of this time he had led an extremely active life, often being in the saddle many hours, and had enjoyed excellent health. This was the first time he had seen his urine "dark," and Dr. Duan who examined it found a small quantity of blood. He had been therefore thirty-seven months without any urinary symptoms and ten months without treatment. He now began the injections again, using three-quarters of a grain.

1896, April 5th.—The patient had gradually increased to $\frac{1}{2}$ grain, and persevered with it for a year, and since then (June, 1895) he had done nothing. To-day he saw a trace of blood, and at once resumed the injections, having been hitherto free for eighteen months.

1897, January 4th and 5th.—He continued the last course until May, 1896, using as much as 2 grains without inconvenience. After a month slight traces of blood were seen on both these days. He writes, "I immediately resorted to the injection with perfect success."

1898, May.—After many months without treatment, blood appeared in larger quantities than usual, though not so large as in the beginning of 1891. The same plan was adopted as before.

1899, June 14th.—Traces of blood were noticed once or twice a week until the beginning of November, when he passed a large "particle," which was pronounced by Dr. Duan to be papillomatous. Shortly after this the blood ceased, and there has been very little since. In every way he is in very good health, and exceedingly active.

CASE III.

1891, July 15th.—Aged 60. Came with Dr. Statham, of Cheddar. Six months ago he had noticed the urine dark, and it has been rarely quite clear since then. Four days ago he passed much florid blood on one occasion only. There have been no other urinary symptoms, with the exception of slowness and feebleness of stream. No shreds of tissue could be obtained from the bladder in the usual way then, but later, while the patient was under an anæsthetic for a small operation, a specimen of papilloma was removed by the lithotrite. He commenced to learn the treatment at once, using half a grain of nitrate of silver to 4 ounces of water.

1892, February 13th.—Notwithstanding the daily injection of $\frac{1}{2}$ gr. the bleeding had continued in small quantities, though intermittently, until November 6th, 1891, but from this date until now he has only seen blood once.

1892, December 26th.—Traces of blood have been seen on five or six occasions, including to-day, and he has increased the injection to $\frac{1}{2}$ gr.

1893, May 5th.—He has had an interval of four months without symptoms, and has left off the treatment for three months. Lately the blood has been more frequent, and in large quantities.

1896, October.—Dr. Statham reported that the patient had injected him-

self, using $\frac{1}{2}$ grain during this period. "About every four months he had a return of the hæmorrhage, which quickly yielded to treatment."

1898, July 26th.—Dr. Statham writes that he has been well, taking a good deal of exercise, and free from symptoms with the exception of slightly smoky urine once following influenza.

1899, May 28th.—In November, 1898, he had a slight attack of hæmorrhage, which lasted five days. He at once began the injections, and continued them until February 13th, 1899, and has seen no blood during that period. He now has an attack of cystitis, accompanied by hæmorrhage, from which he is recovering.

CASE IV.

1892, January 26th.—Aged 42. Came to consult Sir Henry Thompson with Dr. Douglas of Newbury. During the last three or four years he had experienced a tickling sensation in the urethra, increased frequency of micturition, and occasional incontinence. Four days previously he had seen a considerable quantity of blood in the urine, which had recurred daily since. A fine specimen of papilloma was removed and examined.

1893, July 18th.—He had made a daily injection, at first under the guidance of Dr. Douglas and then by himself until August, 1892, when, as all the urinary troubles had subsided, no further treatment was adopted. Dr. Douglas reported that he had never had any hæmorrhage up to the time of his death, which occurred in the spring of this year from pneumonia.

CASE V.

1892, February 12th.—Aged 40. Sent by Dr. Smyth of Brockley. He complained of frequency of micturition, a little tickling pain at the end of the penis after the act, and since November, 1891, he has had excessive hæmaturia, which kept him in bed on two occasions for a fortnight. The urine was offensive. A shred of papilloma was obtained in the usual way.

1895, July.—Dr. Smyth had taught him to inject, beginning with a weak solution, and he had continued to do so, at first every day and then irregularly to this time, but all urinary troubles had subsided by September, 1892. He has seen blood lately and has used the injection more freely.

1898, July 25th.—He reports that he has seen no blood for eighteen months and has ceased treatment for a year, and now has no urinary troubles whatever. Previous to this he had some attacks of slight hæmorrhage, he cannot say how many, but they were always overcome by the injection. He is in good health and takes much exercise, lawn tennis and dancing.

CASE VI.

1892, October 29th.—Aged 64. The patient came with retention, caused by a large blood-clot in the bladder. He had experienced difficulty in passing urine once before, in November, 1891, but had seen no blood, and complained occasionally of smarting along the urethra. A specimen of papilloma was secured while relieving the retention. I taught him to inject with the nitrate of silver solution, commencing with one-half grain to the 4-ounce bottle. In ten days' time the bladder had recovered its expulsive power, and the hæmaturia had ceased. The urine was healthy.

1893, December 19th.—He had injected the solution, using $\frac{1}{2}$ gr. daily until May 23rd, every other day until July 21st, and had discontinued it on September 21st. To-day he noticed blood in the urine for the first time since November, 1892, an interval of fourteen months, and at once began to inject.

1894, August 4th.—All traces of blood had disappeared by the end of December, and he left off the treatment on June 23rd. To-day a very small quantity of blood was seen after an interval of seven months.

1896, January 18th.—No treatment had been adopted since October, 1894, and he had only seen very slight indication of blood thirty-six times during this period of fourteen months. As the hæmorrhage had now increased both in frequency and amount he commenced to inject again.

1897, May 18th.—The hæmaturia ceased in March, 1896, and the following month the injections were stopped, and for the last thirteen months he had observed blood only on a few occasions. During the latter half of the time injections of 1 gr. had been made twice a week. He was now suffering from an acute attack of septic cystitis accompanied with severe and continuous hæmorrhage. It lasted for ten days, and was followed by phosphatic deposit in the bladder. I removed some half dozen concretions, the largest the size of a bean. After this, and with the aid of daily injections, he rapidly improved, the urine becoming quite clear and healthy again.

1899, January 7th.—He had continued the treatment for three months, using 1 gr., and then left off. Blood had been seen during the nineteen months, a few times in very small quantities, but had always been completely controlled when the solution had been used with any regularity. The patient is now over 70 years of age and enjoys good health, and is fairly active, complaining in no way of the urinary trouble.

1899, April 8th.—Blood had been seen on a few occasions, and he is now going to undertake a regular course of daily injections for six months at least.

CASE VII.

1892, November 8th.—Aged 38. For two years he had been passing blood every few days, often in large quantities, but had no other symptoms. A fine specimen of papilloma was easily found and examined. He learned to inject himself, finally using $\frac{1}{2}$ gr. The urine was clear.

1893, October 13th.—He reported himself "much better," though he had passed blood in small quantities on 11 occasions. He had injected daily without intermission.

1894, November.—During the past thirteen months he had injected with more or less regularity, but blood has been seen on 27 occasions in small quantities.

1895, September 1st.—There has been no blood since the last report, and he had made no application. To-day again slight indication, and the injection started afresh.

1899, May 2nd.—He had continued the injections for two months, but had never undertaken any treatment since. Sometimes months were passed without seeing any hæmorrhage, then blood has appeared on two or three following days in small quantities, but only when straining at stool, rarely at other times. He is exceedingly active, hunting, etc., and enjoys good health.

CASE VIII.

1894, June 23rd.—Aged 64. A year ago she first saw blood in the urine,

and now complained of increased frequency of micturition, both by day and by night, urgency, severe pain always after the act, increased by movement, and frequent attacks of severe hæmaturia. The urine was offensive and contained blood. As no characteristic fragment of tissue could be obtained in the usual manner, she was anaesthetised, placed in the lithotomy position, and a speculum introduced through the urethra into the bladder after dilatation. Dr. Spencer was present, and kindly gave me his advice as to this method of examination. A sessile tumour, extending over an area of 1.75 sq. in. and 0.75 in. in thickness, was easily seen. The small portion of tissue removed for microscopic examination proved to be papilloma, the surface being coated with phosphates, but the base of the tumour was most probably of a malignant character.

1894, August 9th.—She had injected twice daily, using $\frac{1}{2}$ gr., never stronger, as even this caused discomfort sometimes. She still had some pain after micturition, but the frequency had decreased, and there had been intervals of five or six days without hæmaturia. The urine was still offensive. She returned to Salisbury under the care of Dr. Blackmore.

1896, June 27th.—She had carried out the injection with 1 gr. intermittently, using it twice a day, but had never been quite free from pain nor hæmorrhage. On one occasion only had it been severe and lasted two days. The other urinary symptoms were present but not so urgent.

1897, October.—Dr. Blackmore reported that she had been fairly well till now, all the urinary symptoms had improved, but she had never been entirely free from them though the hæmorrhage had never been severe. During this period Dr. Blackmore had tried weak solutions of copper sulphate with success, but the silver had been far more frequently applied.

1898, April.—Dr. Blackmore reported her death from exhaustion. The cystitis had gradually increased from October, 1897, and she had suffered much pain lately only relieved by narcotics. The tumour, which could be felt bimanually, had increased to the size of a tennis ball.

CASE IX.

1896, July 18th.—Aged 37. This patient was sent by Dr. Smyth of Brockley. He had first noticed blood nine months ago, when it had continued for three weeks every time water was passed. Since that time he had never been free from it for longer than a fortnight, and, in addition, he complained of a slight tickling along the urethra towards the end of the act of micturition. Dr. Smyth taught him to inject himself with 1 gr.

1897, May.—He had made daily injections till January 31st, 1897, and had then ceased, and had had no hæmaturia since the middle of December, but to-day slight indications of blood were seen.

1897, September 30th.—Blood had been seen frequently, sometimes every day, and he had consequently commenced the injections in June, continuing them until now. He now has an attack of acute cystitis, with severe hæmorrhage, every time he micturates.

1898, February.—The cystitis has subsided, but slight hæmaturia is constantly present though the urine is in other respects clear and healthy. He is to continue the treatment.

1898, November 5th.—He had injected intermittently since his last report, sometimes every day for a fortnight, and had then left off for three weeks. The hæmorrhage has always ceased for a considerable time immediately after a course of injections, though while using them a drop or two of blood had been generally noticed daily at the time of catheterisation.

1899, April 28th.—The patient had commenced a systematic course of treatment from the last date, beginning with 1 gr., and reaching a maximum strength of 2 gr. towards the end of that month. Hæmorrhage in small quantities had occurred almost daily at the time of catheterisation until January 17th, 1899. From this date until the present time the bleeding has been much more intermittent, and seven or eight days have elapsed without any blood being seen. He intends continuing the treatment for another six months.

CASE X.

1897, April 6th.—Aged 43. The patient passed blood for the first time early in January, 1897. The hæmorrhage lasted two or three days. It recurred two weeks later, and had continued almost daily, and on every act of micturition, ever since, sometimes in considerable quantities. He complained of slight pain in the urethra both during and after micturition. He had been for some weeks in hospital, and an operation on the kidney was contemplated, as it was thought the hæmorrhage arose from that organ. I did not think the treatment by injection was suitable for his case, as his occupation—that of a yacht's seaman—would seriously interfere with it being carried out properly. He, however, declined operation, and I taught him to inject.

1898, November 2nd.—He reports, in reply to a letter, as follows: "I injected daily until July, 1897, and then once a week until November, 1897. Once a month till July, 1898, and not since. I have not seen any blood since June, 1897, and the water keeps good. I have no pain at all. I was at work in the English Channel from December, 1897, until February, then I found the yacht, March 1st, 1898, and am still at work on board of it, laying up at Southwick. I have my health good."

1899, May 5th.—He writes he had no hæmorrhage until March 15th, 1899, an interval of 20 months, when he had passed a quantity of dark blood with great pain. Injections were at once resorted to, and the bleeding ceased. He is now without pain, and quite well.

CASE XI.

1897, November 9th.—Aged 48. Sent by Dr. Menzies, of Worksop. He first saw blood in his urine in February, 1895, a few drops after micturition. In December, 1896, he had daily bleeding from the penis for 14 days, independent of micturition. October 19th, 1897, he had severe and continuous hæmorrhage, which caused retention on October 21st, and was relieved by the aspirator. There was a little blood in the urine when he called, but he had no other symptom. Several specimens of papilloma were found and examined.

1898, May 19th.—Dr. Menzies taught him to inject daily, commencing with $\frac{1}{2}$ grain, and increasing to 2 grains, until February 14th, when he did so every other day. Blood had ceased on November 17th, and none was seen until January 2nd, and again on February 2nd and 4th, frequently during April, and he now sees it once or twice a week.

1899, February 28th.—He had made injections very irregularly, and the blood had never ceased. For three weeks or more he has had much pain,

frequency of micturition, increased hæmorrhage, and septic urine. His condition was very unsatisfactory.

1899, May 14th.—Dr. Menzies reported that "owing to cystitis and increasing obstruction, suprapubic cystotomy was performed on March 25th, and a permanent opening established for drainage. A large growth was found at the base of the bladder, widely infiltrating the muscular coat." The portion of the tumour removed, and which Dr. Menzies kindly sent up, was examined by Dr. Sidney Martin and proved to be a so-called squamous epithelioma, with a fibre cellular matrix, the surface being covered with papillomatous tissue. The patient died on this day from congestion of the lungs.

CASE XII.

1898, June 2nd.—Aged 69. Three months ago he had continuous hæmaturia for three weeks. This recurred in May, and has persisted since. He had no other urinary symptom. His condition was unsatisfactory for he was weak and blanched from loss of blood; and large shreds of papilloma were passed. I kept him in bed, injecting him myself with the silver solution, but only with 1 gr. to the 4 ounces of water. No improvement whatever was noticed in the urine for the first week. It was always thick with blood, and as he was evidently losing ground, I proposed to do suprapubic operation for the removal of the tumour, still continuing the injections, but three days later—the day fixed for the operation—the hæmorrhage ceased, and surgical interference was postponed. I kept him under personal observation for a fortnight longer, injecting him daily, and as no blood was seen he returned home with a nurse to continue the injection treatment there.

1899, January 12th.—I heard that he had continued the injection, using 1 gr. of nitrate of silver daily, until October 23rd, since which he had made no application at all, and that he had never seen any blood. He was in good health and was much stronger.

1899, May 9th.—He reports himself quite well and free from all symptoms.

NOTES.

¹ A solution of 1 in 12,000 perchloride of mercury is a good preservative fluid for a short time. ² I am indebted to Dr. William G. Savage, assistant to the Professor of Pathology at University College, for a series of experiments on this point. He writes: "Water at 150° F. even for half a minute, is a reliable steriliser of catheters for ordinary work."

NOTE ON THE BLOOD IN A CASE OF BERI-BERI.

BY

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DURING the last few years we have been investigating the physiological action of choline and neurine, with special reference to the pathology of general paralysis of the insane. Our results will be fully published with illustrative tracings in the *Philosophical Transactions of the Royal Society*.¹ One conclusion we arrived at may be however briefly mentioned, namely, that the cerebro-spinal fluid of these patients produces when injected into the vascular system of animals (cats, dogs, rabbits) a considerable fall of blood pressure; and this is due to the presence of choline. This alkaloid doubtless originates from the lecithin of the disintegrating nervous tissues. The nearly related alkaloid neurine is not present; it is more toxic, and its most marked effect on the circulation is a preliminary fall of blood pressure (mainly cardiac in origin), followed by a great rise of pressure due to constriction of peripheral blood vessels. The fall of arterial pressure produced by choline is partly of cardiac origin, and partly due to the dilatation of the peripheral vessels, especially in the intestinal area. It may also be mentioned that the blood of these patients, removed by venesection during the epileptiform seizures, which form a prominent symptom of the disease, contains the same alkaloid; our proof that the toxic material both from blood and cerebro-spinal fluid is choline were partly chemical and partly physiological, that is, the effects of the material were exactly the same as those of minute doses of choline or of choline hydrochloride.

In the course of this investigation we had occasionally opportunities of testing the action of other fluids; thus we found that the alcoholic extracts² of normal blood, normal cerebro-spinal fluid, and ordinary serous effusions contain no choline and produce no results on blood pressure.

It is, however, to a specimen of blood from a case of beri-beri that we wish, in this note, to draw particular attention. We are indebted for the specimen to Dr. Patrick Manson. The blood was removed from the patient by venesection, undertaken with a view to relieve right heart distension, was immediately mixed with alcohol, and it was this mixture which Dr. Manson kindly forwarded to us.

Before we injected the material, the mixture was filtered; the filtrate was evaporated to dryness at 40° C., and the