margin of the fossa. The margins of the longitudinal fissure of the brain were pretty firmly adherent in the anterior half, and the tips of the frontal lobes were adherent to the dura mater. There were evident signs of old meningitis at the base. The pia arachnoid was thickened and opaque, especially over the optic nerves, chiasma and tracts, the crura and pons. The optic nerves were dull grey, and the chiasma and tracts distinctly changed in colour. There was no marked diminution in size. The left third nerve was greyer than the right, and more flattened. The corpora quadrigemina were normal in size and appearance." Scattered tubercles were found in the brain. The fracture does not appear to have involved the optic foramen.

A man aged about 30 was brought to me at St. Thomas's Hospital in 1888, complaining of loss of sight in the right eye. A few months previously he had been an inmate of the hospital suffering from concussion and an injury to the right frontal region (? fracture), but had not complained of his eyesight. Mr. Lawford reported atrophy of the disc, and the eye was quite blind.

Mr. Nettleship¹⁶ says on the subject: "But in the more common cases the accident is an injury to the head, probably causing fracture of the roof of the optic canal, with crushing of and hæmorrhage into the nerve, or perhaps occasionally tearing of the nerve on the brain side of the canal. Both conditions have been shown to occur in fatal cases of fracture of the base of the skull."

Another possible cause for blindness after these injuries is the occurrence of hæmorrhage into the sheaths of the optic nerves. In none of the *post-mortem* records of cases in the series here brought forward was fracture in the neighbourhood of the optic foramen found, but in eight, where the damage to the base was severe, blood was found extravasated in the sheaths of the nerves. And in one at the end of eight days there was also slight neuritis. It is a remarkable fact, and one of considerable importance, that in these cases of injury to the head which I have related, and in which optic neuritis was found on ophthalmoscopic examination, if the neuritis was found in both eyes complete recovery ensued, but if after an injury to the frontal region a condition of neuritis developed in one eye only, the disc presented at a later date complete atrophy, and the patient remained permanently blind on that side. Paralysis of one or more branches of the third nerve may ensue as a consequence of injury to the head, but it was very rarely seen, the difficulty in movement presented by various ocular muscles appearing to be the result of hæmorrhage, and the interference which it caused to their action, rather than to any injury to the nerves supplying them. When paralysis of the third nerve was present it was due to compression by an extravasation of blood at the base. In one fatal case in which it was not possible to get a *post-mortem* examination paralysis of the sixth nerve was noticed on admission, soon after the accident. In five patients who recovered this paralysis was present when they were first examined; of these the injury had been very severe in all, and the squint continued without sign of improvement when they passed from observation. In one of these it was associated with optic atrophy, and in one with simultaneous loss of power in the facial nerve of the same side. In all a fracture of the middle fossa was diagnosed. Of the four others in whom it appeared at a later date—on the second, third, fifth, and thirteenth day—the manifestations of injury were severe, and the squint continued without improvement when last seen, with the exception of the patient in whom it appeared on the third day, and was associated with proptosis, and later with optic atrophy; in his case there was gradual improvement in the squint. It is probable that when the nerve is paralysed from the first the paralysis is due to rupture of the nerve, though a case recorded¹⁷ does not appear to support this. In that case it is stated that the squint did not develop until three weeks after the injury, yet at the *post-mortem* examination the sixth nerve was found snapped across. One can hardly think there was no paralysis before three weeks after the injury. Although in these examples the state of the nerves did not, with one exception, improve under observation, it is the experience of others that in several instances power has been gradually regained.

In a child, aged $3\frac{1}{2}$ years, suffering from concussion, temporary paralysis of this nerve was observed for a period of six days, but with reference to squint in children, the statements of the mothers as to its absence before the head injury do not always agree with what is said by other relatives. There is another thing to be borne in mind, and that is the possibility of the squint being a

manifestation of syphilis. An old patient of mine, who had suffered severely from tertiary manifestations some years ago, recently fell forwards accidentally and struck his forehead against the mantelshelf in his room. Three days afterwards double vision gradually developed, which made it difficult for him to move about anywhere. Under iodide of potassium he recovered at the end of two months. That such a symptom as strabismus is important from the interference with vision that may follow it is well known, and as the prognosis depends much on the date of its appearance, it should be decided by the medical man when he first sees the patient whether strabismus is present or not, for the question of damages in a law court may depend much on this point, as in a case recently related to me.

Paralysis of the facial nerve is an accompaniment of many fractures of the base; indeed, like hæmorrhage from the ear, it may be regarded as a most valuable sign of fracture in the middle fossa. Mr. Pick,¹⁸ in his remarks on some cases of fracture of the base, states that in thirteen well marked instances this symptom was present in ten, and that it developed at once in two and in a period of from two to six days in eight. It was not met with in anything like this proportion in the cases under my observation; in only fifteen was paralysis of the facial nerve sufficiently marked to attract attention, if we exclude two in which the patients were the subjects of old hemiplegia. In six the paralysis was present on admission, and persisted when the patients (four in number) who recovered were able to leave the hospital. In the two fatal cases it was found that the fracture which extended through the internal auditory meatus had produced considerable laceration of the nerves. In the others it appeared as follows: On the second day in a man aged 31, after severe hæmorrhage from the ear, in whom the fracture was proved to have passed across the internal auditory meatus without lacerating the nerves. On the fourth day in a man aged 48, who recovered. On the fifth day in a man aged 29, who died from erysipelas and pyæmia. On the eighth day in a man aged 62, who died from delirium tremens. The fracture involved the internal auditory meatus, but no coarse lesion of the nerves was seen. On the tenth day in a boy aged 10. There was much œdema of the scalp and suppuration in a scalp wound at the time. The paralysis had nearly gone in a month. On the tenth day in a man aged 23, preceded by deafness the day before. The paralysis had nearly disappeared in a fortnight. On the sixteenth day in a man aged 37, with an attack of erysipelas. The hæmorrhage from the ear had been very free at first. The paralysis was transient. On the eighteenth day in a man aged 40. Deafness before the accident increased during the period of hæmorrhage, four days. The paralysis lasted six days, and during the time deafness was more manifest.

OBSERVATIONS

ON

THE TREATMENT OF PERNICIOUS ANÆMIA

BASED ON A STUDY OF ITS CAUSATION

WITH NOTES OF A CASE.

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(Continued from page 1.)

CAUSATION.—EXCRETION OF AROMATIC SULPHATES.

THE further series of observations I made on the urine in the above case related to the cause of the extensive blood destruction prevailing in this condition. I concluded as the result of my first investigation, for reasons I have already indicated, that to produce a condition of blood and of the liver such as was found in pernicious anæmia, the action of a special poison was necessary. With regard to the nature of the poison or poisons thus generated, I stated that my observations up to that time had not supplied me with any definite information. From analogy, however, afforded by the action of the toluylene-diamine, more especially from the limitation of its action to the portal blood, I concluded that "the poison was probably of a cadaveric nature produced within the gastro-intestinal tract—in excessively small

¹⁶ *Loc. sup. cit.*

¹⁷ *Journal de l'Expérience*, 1843.

¹⁸ *JOURNAL*, 1865, p. 530.

quantity, however, and not necessarily constantly"; and that "the destruction of blood was effected by the action of such poisons absorbed from the gastro-intestinal tract."

In the present case, therefore, I directed my special attention to such characters of the urine as might be capable of affording an insight into the nature of the changes occurring within that tract. Considering how important a part is played by putrefaction in the changes within the intestinal tract below the duodenum, my first thought naturally was that excessive putrefactive change might be the cause of the condition, and might lead to the formation of such poisons. We have a reliable index as to the amount of putrefaction within the intestine in the excretion of aromatic compounds in the urine—compounds, that is to say, such as phenol, indol, skatol, cresol—derived from the disintegration of proteid material in the process of putrefaction. These compounds do not appear in the urine as such, but in combination with sulphuric acid in the form of ether sulphates, chiefly of potassium. Since the sulphuric acid excreted in this form is also derived from the sulphur of the proteid constituents of the food, we have a comparatively easy and ready means of determining the total excretion of aromatic compounds in the urine by determining the quantity of sulphuric acid with which they appear in combination. There are thus two forms in which sulphuric acid is present in the urine; (A) as free acid combined with the salts of the food, and derived directly from these salts; (B) as aromatic sulphuric acid, in combination with the aromatic compounds of the urine, and derived from the sulphur of the proteids of the food.

In health the ratio of these two to each other—of A to B—is fairly constant. The quantity of free sulphuric acid usually exceeds that of aromatic sulphuric acid in the proportion of 10 to 1, and this ratio remains fairly constant independent of all changes of diet. The relation is affected in all conditions in which the amount of putrefactive change within the small intestine is in any way modified from the normal. In obstruction in this portion of intestine putrefaction may be so increased that the ratio of A to B becomes equal, or the amount of aromatic H_2SO_4 (B) may even exceed the free H_2SO_4 (A). On the other hand, by clearing out the intestines with purgatives, such as calomel, it is possible, for the time at least, to cause the total disappearance of B from the urine. In such cases there is not only a disturbance in the ratio of A to B, but also in the total excretion of each. The former is, however, the more important, as the quantity of each is dependent to a great extent on the quantity of food ingested. The important point is that in health, whatever the quantity of food taken, the amount of putrefaction which occurs in the proteid constituents bears a certain more or less constant relation to the amount ingested—a relation expressed by stating that the amount of aromatic H_2SO_4 excreted in the urine stands to the amount of free H_2SO_4 similarly absorbed and excreted as 1 to 10; variations from 1 to 7 up to 1 to 15 being, however, still within the limits of health.

In the following table I have embodied the results of my observations in the foregoing case:

Table showing Excretion of Aromatic Sulphates in a case of Pernicious Anæmia.

Date.	Quantity of Urine in c.c.	Total Excretion of free H_2SO_4 as Barium Sulphate.	Total Excretion of free H_2SO_4 (A)	Total Excretion of Aromatic H_2SO_4 as Barium Sulphate.	Total Excretion of Aromatic H_2SO_4 (B)	Ratio of A to B.
1889,		Grammes.		Grammes.		
March 11 ...	1,100	1.496	0.629	0.484	0.203	3 to 1
" 18 ...	600	1.251	0.526	0.261	0.109	4½ to 1
" 22 ...	1,050	1.438	0.604	0.262	0.110	5½ to 1
" 23 ...	1,030	1.731	0.738	0.300	0.126	5.7 to 1
April 15 ...	600	3.030	1.274	0.276	0.116	11 to 1
" 22 ...	—	(0.252 per cent.)	—	(0.030 per cent.)	—	8½ to 1
May 2 ...	1,100	2.090	0.879	0.275	0.115	7.6 to 1
" 6 ...	1,000	2.505	1.053	0.405	0.170	6.1 to 1
" 10 ...	900	2.034	0.855	0.342	0.153	6 to 1

The method I used for estimating the sulphuric acid was Salzkowski's modification of Baumann's original method. The free H_2SO_4 is precipitated from the urine at once on adding a solution of barium hydrate; while the aromatic H_2SO_4 is only precipitated after the aromatic compounds have been broken up by heating

with strong hydrochloric acid. Each variety of H_2SO_4 is thus obtained in the form of a barium sulphate; and the actual quantity can be determined by subsequent ignition and weighing.

The results recorded in the preceding table bring out certain interesting facts. They indicate, first of all, that the absolute amount of putrefaction occurring within the intestinal canal in pernicious anæmia is not in excess of the normal. The amount of aromatic H_2SO_4 excreted in health varies somewhat according to the amount of food taken. The average daily excretion, however, is about 0.25 gramme. In the above case the excretion never reached this amount, although in the first instance it closely approached it (0.203). Of far greater importance, however, as I have stated, is the ratio of free to combined H_2SO_4 —of A to B—in such cases; and the above figures indicate a disturbance of the normal ratio of very considerable extent and significance. In the first instance the ratio was 3 to 1 instead of the normal 10 to 1, this result indicating that of the very small quantity of food taken at this time (as evidenced by the small quantity of free H_2SO_4 excreted), the quantity destroyed by putrefactive change was three times greater than that which should have occurred. Under the treatment commenced at this time—carbohydrate instead of a more nitrogenous diet—the ratio steadily but slowly improved, till finally, a month later, it had reached the normal—namely, 11 to 1. This alteration was coincident with improvement in the patient's condition.

It was at this time that the patient felt and looked better than at any time observed during the latter part of his illness. He was not only taking more food, as evidenced by the steady increase in free H_2SO_4 from 0.629 gramme to 1.274, but he was utilising more of it for purposes of nutrition, as evidenced by the steady diminution in aromatic H_2SO_4 from 0.203 to 0.116. At the same time the colour of the urine was more normal than at any time observed. On April 15th, for the first and only time, it could scarcely have been distinguished from that of health. A few days later, however, an exacerbation occurred, and the urine rapidly regained its former high colour. From this time onward till death the disturbance in the ratio of A to B was less marked—8 to 1, 7½ to 1, and then 6 to 1. This disturbance was due, be it noted, more to an increase in the excretion of aromatic H_2SO_4 (B)—to a relative increase, therefore, of putrefaction—than to any great diminution in the quantity of free H_2SO_4 (A). The former, although relatively excessive, was, however, in no way sufficiently marked to be credited with being the cause of the special symptoms of so well-marked a disease.

EXCRETION OF PTOMINES.

At the same time that I made these observations I also made a further series with a view to determine whether any special bodies of the nature of cadaveric poisons or ptomines were present in the urine. I had already for some time been engaged in investigating the nature of the ptomines formed during putrefaction, and had been able to isolate certain of them in large quantity and in a chemically pure condition.

The method I employed was that of Brieger, modified in its later stages by a method I had learnt while working with Professor Hoppe-Seyler, of Strassburg, based on certain observations of Baumann and Udranzky. These last observers have recently shown that benzoyl-chloride forms remarkably stable compounds with all bodies of diamine nature, and certain of the more common ptomines, such as cadaverine (penta-methylene-diamine) and putrescine (tetra-methylene-diamine) belong to this group of bodies. The method I employed was briefly the following. After evaporation of the urine to dryness, and removal first of various insoluble salts by extracting with alcohol, and, secondly, of various extractive matters with other salts, such as sulphates, phosphates, etc., by precipitating with alcoholic solution of neutral acetate of lead, the remaining alcoholic solution was precipitated with warm alcoholic solution of mercuric chloride. In this way most of the organic bases present were thrown down in the form of insoluble mercuric chloride compounds. Some, however, always remained in solution. Both precipitate and filtrate were therefore kept, and treated separately—the mercury removed after driving off the alcohol, and the solution remaining, after being rendered strongly alkaline by addition of 10 per cent. caustic soda solution, then treated with benzoyl chloride.

I succeeded by the above method, in isolating from both precipitate and filtrate a certain quantity of a double benzoyl compound in a perfectly pure condition. The method I adopted was to

treat the urine of different days—sometimes of many days together—in the manner above described, and then treat the different portions with benzoyl chloride. In some instances the hydrochlorate salts of the nitrogenous bases were converted into double platinum salts or picrates. The benzoyl-chloride method yielded the best results, as it was also the one most easily applied. From a number of different portions of urine thus treated during the last two months and a half of the patient's illness I obtained a very small quantity a benzoyl compound possessing very definite crystalline characters and equally definite physical properties. It was extremely soluble in alcohol, insoluble in water. It crystallised out of alcohol in form of long fine needles, arranged in rosette-like bunches. On determining the melting point of the first specimen thus isolated, I found this to be between 171° and 173° C. A specimen from another quantity of urine had a similar melting point at first. On further purification I obtained it constant between 174° and 175° C. From other specimens of urine I obtained a similar compound. In respect of crystalline form and melting point this body is identical with the double benzoyl compound of putrescine (tetra-methylene-diamine), a ptomine first isolated by Brieger from putrefying meat. The melting point of this compound, when absolutely pure, is 175° to 176° C.¹ Slight impurity tends always to lower the melting point several degrees. Thus the melting point of the double benzoyl compound of putrescine, obtained by Baumann and Udranzky from the urine in a case presently to be referred to, was 170° to 173° C. After repeated crystallisation and purification its melting point remained constant at 175° to 176° C. On comparing the compound I had obtained from the urine with a similar compound of putrescine I had prepared from putrefying meat, I found them in all respects identical. In most cases this ptomine—as to the identity of which with putrescine I have myself no doubt—was obtained alone. In other samples of urine it was present along with another ptomine, which also formed a double benzoyl compound, with very definite crystalline characters—long, elongated, rectangular prisms. Owing to the small quantities at my disposal I was unable to effect the separation of this latter substance. The characters of its crystalline compound were, however, those of cadaverine (penta-methylene-diamine), another ptomine always obtained from putrefying meat, and large quantities of which I had in my possession. These two ptomines—cadaverine and putrescine—are usually found in association, sometimes the one, sometimes the other, preponderating. In ordinary putrefaction the cadaverine, according to my observations, greatly preponderates.

Lastly, from one of the specimens of urine I isolated a compound in a perfectly crystalline form, of whose identity I have not been able to assure myself—its double benzoyl compound, crystallised in long rectangular prisms, resembling those of the cadaverine compound. The melting point of this compound lay between 70° and 80° C.—a wide margin, indicating that more than one body was present. From its behaviour in other respects, I conclude that it was not cadaverine, whose benzoyl compound it most resembled. The melting point of the latter is 129° to 130° C. It will remain for my further observations to show what this body is. As I have not met with it in any of my observations on the ptomines of putrefaction, I am inclined to believe that it is a special diamine body.

As to the significance to be attached to the presence of these ptomines in the urine in this case, I desire to speak with all reserve. I am inclined, however, to attach not a little, and for the following reason—that putrescine (as also cadaverine) belongs to a group of nitrogenous bases, so-called "ptomines," formed from proteids by the action of bacteria, and never formed as products of the metabolism of the tissues themselves. Neither of them has been found in the urine in health,² nor are they met with in disease,³ even in conditions in which they might be expected to occur. Udranzky and Baumann examined the urine in cases of scarlet fever, diphtheria, typhoid fever, pneumonia, tuberculous peritonitis, intestinal obstruction, and extensive suppuration—all of them conditions in which there is an increase in the putrefactive changes within the tissues or within the intestinal tract—without finding a trace of them present. In the foregoing case we have already seen that there was no such increase. It is obvious, therefore, that the action of ordinary putrefactive organisms cannot account

for the appearance of these ptomines in the urine in this case or in other cases since they are absent when putrefaction is increased, and are present when it is not increased.

Since, however, they are only formed by the action of micro-organisms, I conclude that their presence in the urine in the present case points to the action of special micro-organisms. And this is the conclusion also arrived at by Udranzky and Baumann in the only other condition in which these two ptomines have hitherto been found in the urine. In a case of cystinuria these two observers found cadaverine and putrescine in large quantity both in the urine and in the faeces; and Brieger has since confirmed this observation in two other cases of this peculiar condition. Their presence was in no way connected with excessive putrefactive change, for in their case as in the present one there was no increase in the excretion of aromatic sulphates, nor any unusual disturbance in the relation of the free sulphates and aromatic sulphates.

What, then, is the relation between the excretion of these bodies in the urine and the well-marked symptoms observed in the foregoing case of pernicious anæmia? Neither putrescine nor cadaverine possesses any markedly poisonous properties. Even if present in much larger quantity than they were, they could not, therefore, be held responsible for the production of these symptoms. If further evidence on this point were wanting, it would be afforded by the case of cystinuria referred to, in which they continued to be excreted in the urine for over a year without the health of the patient being in any way materially affected thereby. They derive their importance, therefore, from this circumstance, now fully established by many observations, that they are the common products of bacteria differing widely in pathogenic qualities; that, while their formation is sometimes unaccompanied by that of any other poisonous bodies (ordinary putrefaction), it may, on the other hand, be accompanied by that of very active poisons (cholera). The character of the organisms more than that of the conditions under which they act, it is I find, that determines the formation of active poisons. This being the case, the presence of even non-poisonous ptomines such as the foregoing in the urine, pointing, as we have seen it does, to the presence of special micro-organisms in the alimentary tract, has a very special significance. It indicates the existence of the one condition more than any other favourable to the production of other and more poisonous ptomines.

If we now consider whether any of the symptoms observed in the foregoing case pointed to the action of such poisons, we come upon certain very interesting facts pointing very directly to such a conclusion. The exacerbations from which the patient suffered from time to time presented all the phenomena of toxic poisoning, whether regard be had to the more nervous phenomena—the sudden onset of drowsiness, the contracted pupils, the slight fever, and the sweating; or to the more local manifestations of the action of such poisons: the intestinal disturbance, and the obviously increased destruction of blood which always attended such attacks. The latter was manifested, as we have seen, by (1) the high colour of the urine and the appearance of urinary pigments and chromogens other than those of health; (2) by excretion of hemoglobin through the kidneys, and its appearance in the urine in the form of granules of blood pigment; (3) by increase in the pigments of the faeces; and (4) by more marked lemon tint, from the presence of a special pigment in the subcutaneous fat.

All these phenomena were so closely related to one another in their occurrence and their degree, and were always marked by such an increase in the patient's weakness as to point, in my opinion, to the closest possible connection between them—the weakness being due to an excessive destruction of blood caused by the absorption of specific poisons from the alimentary tract, the more stable and less toxic of these being excreted at the same time in the urine.

So closely did certain of the phenomena, more especially those connected with the nervous system—the drowsiness, sudden in onset and of short duration, in a person intellectually very bright and of a disposition naturally keen and active, the contraction of pupils and the perspirations—resemble those of a poison of the nature of muscarine, that even at the time, and before I was aware of the presence of certain ptomines in the urine, I regarded them as toxic in their character, and began the administration of atropine with the view of antagonising, if possible, their action.

While this failed, as might have been anticipated, in modifying in any material way the further course of the disease, it was suc-

¹ Baumann and Udranzky, *Zeitschrift f. physiol. Chemie*, xiii, June, 1889.

² Brieger and Stadthagen, *Berl. klin. Woch.*, 1889.

³ Udranzky and Baumann, *op. cit.*

cessful in modifying certain, at least, of its symptoms. During the last weeks of his illness there was an entire cessation of the intestinal symptoms and perspiration which at first proved so troublesome, and, at the same time, so weakening in their effects.

That the alimentary tract was the seat of production of these poisons there cannot, I think, be any doubt. Apart from the prominence of the intestinal symptoms in the case—especially on the occasion of these attacks—the observations of Udranzky and Baumann, in the case of cystinuria referred to, in which they found the ptomaines in large quantity in the fæces, leave no room for doubt on this point.

In the present case the marked inflammatory changes, both old and recent, found in the mucous membrane of the stomach point to that, rather than to any other portion of the alimentary tract, as the probable seat of formation of the poisons responsible for these symptoms. The inflammation was at parts localised and of the most intense description, the active proliferation of the glandular cells and the infiltration with leucocytes recalling at once the similar appearances frequently presented by such glandular structures as the kidney, when the seat of a localised infection with micro-organisms. Furthermore, the swollen, pinkish, translucent appearance of the small lymphatic glands lying on the wall of the stomach itself, and under ordinary circumstances scarcely visible to the naked eye, pointed to some recent as well as long lasting irritation in the stomach wall itself. I am disposed, therefore, to regard the gastric mucosa as the seat, not only of the primary infection, but also of the subsequent development of the specific micro-organisms in the present instance, the affection of the tongue being probably of the same nature as that of the stomach. There was a definite history of infection in the case, all his weakness dating from the time he was exposed to insanitary influences. The infection was favoured, in the first instance, by some unhealthy condition of the stomach and tongue; for it is interesting to note that some years previous to the onset of his illness he had suffered from some affection of the stomach, stated then to be "gastritis"; and that although the condition of his tongue never troubled him till after the onset of his weakness, he expressly stated that for some time before he had suffered at times from some uneasiness in the tongue. Successful infection having once occurred, favoured doubtless by these conditions, the history was no longer, or even primarily, one of gastric trouble, but one of steadily increasing weakness, with all the symptoms we have learnt to regard as characteristic of pernicious anæmia.

This conclusion derives a special interest from its bearing on the view I formerly expressed as to the nature of the relationship between pernicious anæmia and changes the most frequently found in association with the disease. These changes include amongst others malignant disease of the stomach, atrophy of gastric glands, gastritis, degenerative changes in the nerve plexuses of the intestine, and, lastly, the presence of intestinal worms, and when present have usually been regarded as the cause of the disease with its attendant symptoms. With regard to all of them I found that "as the essential morbid change in the disease they could not possibly be regarded;" that "however important atrophy of the gastric glands and other changes in the gastric mucosa may be as etiological factors.....they cannot be regarded as the essential anatomical lesions underlying this form of anæmia, even in those cases in which they are found present;" that "malignant disease and other gastro-intestinal lesions are not fitted in any way to account for the peculiar features of this as distinguished from other forms of anæmia." "With regard to them all.....it is necessary to assume that there have been super-added certain anatomical changes essential to pernicious anæmia, on which the features of pernicious anæmia depend." What that special change is I showed to be an excessive destruction of blood caused probably by the action of specific poisons absorbed from the intestinal tract.

The evidence adduced in the foregoing case supplements and confirms to the full the conclusions thus arrived at, and in the light of the observations just recorded as to the presence of ptomaines in the urine, for whose formation the action of specific micro-organisms is necessary, it is, I think, justifiable to draw the conclusion I now would venture to do, that the special factor required to initiate the symptoms peculiar to the special disease—pernicious anæmia—is the presence, under certain favourable conditions, of organisms of specific nature within the gastro-intestinal tract.

These conditions may, I conceive, be either local and permanent

—malignant disease, various forms and degrees of gastritis, with atrophy of gastric glands; or general and removable—a specially unhealthy condition of mucous membrane of stomach and intestine induced by the presence of intestinal parasites, or by prolonged bad nourishment.

TREATMENT.

The object of my investigations into this disease has been by elucidating its true nature to establish a basis for its rational treatment.

In the light of the results obtained, I think it is possible now to formulate the indications for such a treatment. These are, I consider, briefly two:—

1. *To remove the Cause, with the attendant Gastro-intestinal Conditions favouring its Operation.*—This indication of treatment can only be successfully fulfilled when the local conditions favouring its operation can also be removed. The cases belonging to this group are such as have been recorded by Rayher, Runeberg, and others, where recovery has rapidly followed the removal of worms—both *trichocephalus latus* and *anchylostoma duodenale*—from the intestinal tract. The most important point, therefore, to be attended to in diagnosis, after the true (hæmolytic) nature of the anæmia has been recognised, is to determine what the favouring condition is. In the hope that it may be an unhealthy condition of the mucous membrane of stomach or intestine induced by the presence of intestinal worms, free movements of the bowels should always be encouraged in the earlier stages of the disease.

Where it is recognised to be of a more permanent character—for example, gastritis, atrophy of mucous membrane of stomach—the problem of treatment becomes much more difficult. It is in such cases that the advisability of washing out the stomach will have to be considered. Such a treatment was first suggested by Sandoz on the view that certain of the symptoms were those of indigestion, and that products formed as the result of indigestion might be in this way removed. I have shown that these products are of an entirely different character from those had in view by Sandoz, and further, that they are formed not so much, if indeed at all, in the contents as in the walls of the stomach itself. How far such a plan of treatment will prove successful under such circumstances may be open to doubt. It is one, however, which I conceive might be adopted with advantage in the earlier stages of the disease at least, and an early diagnosis of the disease is now, in my opinion, rendered possible by the foregoing researches into its nature.

Where neither the cause nor the favouring condition can be attacked directly by methods such as the foregoing, it is still possible to effect the object indirectly. The beneficial action of arsenic in case of pernicious anæmia, first pointed out by Dr. Byrom Bramwell, has now come to be generally recognised. In some cases, and the foregoing is one of these, it altogether fails. Its mode of action has hitherto been usually conceived to be, in accordance with the views prevalent as to the nature of the anæmia, by stimulating blood formation. I conceive that its action in such cases may be more simply explained as an entirely local one on the mucous membrane of the stomach and intestine, but especially of the latter. In the present case it was so remarkably ill-borne at all stages of the disease, that it is permissible to conclude that this was connected with the subacute and acute gastritis present. Any beneficial action phosphorus may have in certain cases is probably to be similarly ascribed to its local action.

The presence of special micro-organisms as an essential factor in such cases naturally suggests the use of drugs having antiseptic properties. The one I have tried, and the one I believe to be the best suited for internal use is beta-naphthol. It possesses in a special degree the two properties essential for an intestinal antiseptic—namely, great disinfecting power, with, at the same time, great insolubility in water; its antiseptic power is three times that of iodoform.

I used it in the foregoing case during the latter few weeks of the patient's illness, too late, however, to derive any benefit from its action. It can be given in doses of 5 grains thrice daily, suspended in mucilage.

2. The second indication is to combat the symptoms. The most important of these is the excessive destruction of blood induced by the absorption of the poisons. It is the continual drain on the blood thus brought about that causes the intense anæmia and excessive weakness.

The best way of combating this—apart from the removal of the cause—I conceive to be, by regulation of the diet, with a view

to diminish blood destruction so far as possible. The most important factor regulating the amount of blood destruction in health I find to be the nature of the diet, a nitrogenous diet causing a much greater destruction than a farinaceous or fatty one. The blood destruction which occurs in this disease so greatly exceeds, however, that of health, and depends upon the operation of such different factors—the formation and absorption of specific poisons of the nature of ptomines—that the difference between a nitrogenous and a non-nitrogenous diet may be of comparatively little moment. Nevertheless, the results obtained in the present case suggest that such is not the case.

The patient was placed on a more farinaceous diet on March 10th, his previous diet having been made up of beef-tea, extracts of meat, etc. The effect of this treatment was at once noticeable, and was evidenced at once by an entire disappearance of blood pigment granules from the urine, and by the subsequent improvement in the patient's general condition.

After his attack on April 20th I placed him on a purely milk diet. The disease was, however, too far advanced to permit of successful treatment. Under the milk diet the amount of blood destruction as evidenced by the high colour of the urine, continued to be increased. I should be inclined, however, to give a purely milk diet another and a fairer trial than the advanced nature of the present case admitted of. I deemed it desirable, in the light of the results obtained after a change of diet in the present case, to obtain some further data as to the effect of a more exclusively farinaceous diet on the change occurring within the intestine. The observations undertaken to this end were kindly carried out for me by Mr. F. W. Burton. The results he has obtained were recorded by him in full elsewhere, and some of them are of great interest in this connection, and are here, with his kind permission, appended. The method adopted was to determine the relative excretion of free and aromatic sulphates in the urine on (1) a mixed diet, and (2) on a more exclusively farinaceous one.

Table showing Influence of Diet on Excretion of Aromatic Sulphates in a Dog.

Date.	Quantity of Urine in cc.	Free Sulphates, as BA SO ₄ (A)	Aromatic Sulphates, as BA SO ₄ (B)	Ratio of A to B.	Diet.
Feb. 8 ...	434	Gramme. 0.978	Gramme. 0.106	9 to 1	Meat biscuits.
" 13 ...	420	1.386	0.105	13 " 1	
" 18 ...	470	0.639	0.8775	8 " 1	
" 20 ...	340	0.720	0.1258	5½ " 1	
" 22 ...	—	—	—	—	Milk, bread, and oatmeal.
" 24 ...	440	0.673	0.0396	17 " 1	
" 25 ...	440	0.776	0.0484	16 " 1	
" 27 ...	300	0.757	0.0540	14 " 1	
" 28 ...	260	0.824	0.0572	14 " 1	

From the foregoing table it will be seen that while on a mixed diet the ratio of the free to the aromatic sulphates was the on average 9 to 1, the effect of a more farinaceous diet was to reduce the excretion of aromatic sulphates (representing the amount of putrefactive loss occurring in the food within the intestinal canal) by more than one half, with an average ratio of 15 to 1. The result may be expressed in this way—that with an almost equal quantity of food of both kinds, the amount of loss due to putrefactive changes within the intestinal tract was diminished by more than one half by the use of a more farinaceous diet; at the same time there was an increase in body weight. It is on these grounds that I believe good results may be expected from a more exclusively farinaceous diet in cases of pernicious anæmia.

MEMORANDA:

MEDICAL, SURGICAL, OBSTETRICAL, THERAPEUTICAL, PATHOLOGICAL, Etc.

POISONOUS EFFECTS OF EXALGINE.

A. B., aged about 40, a lady of hysterical temperament, has suffered from nervous headache monthly for the last ten or more years, and has been treated with all kinds of drugs, but without

avail. Latterly I have been administering exalgine, commencing with two grains twice a day, which gave great relief. The attack, however, recurred the next month, and two grains every four hours had very little effect, so I increased the dose to five grains twice a day. The first dose was taken at 10 P.M. after supper with great relief to the pain, and the patient slept till 6 A.M., when she awoke and felt headache coming on again, so took another dose and lay down. In about a quarter of an hour she jumped up with a sudden start and scream, and thought she was dying; she had such curious sensations, felt numb all over, fingers and toes tingled and felt dead; eyelids twitched continuously; the whole head felt as if it was swelled, and kept expanding and contracting alternately. There was great oppression in the region of the diaphragm. In a few minutes the patient vomited and ejected the remains of the medicine. She then felt much relieved and lay down and slept, after taking a little tea. Two hours after the patient got up, but felt ill; the headache was slighter, but not gone; the numbness of the fingers and toes remained nearly all day, but beyond this the patient was little the worse for her experience. She went out next day, but says she will be afraid to try the medicine again. I think that this so-called poisoning with exalgine is due to its being taken on an empty stomach, as the former dose was well borne when food was present, so I always order it to be taken after a meal. I give the drug dissolved in tinctura aurantii and diluted. I have found it useful in toothache, facial neuralgia, and in a case of long standing lumbago. No beneficial effect of the drug have I found from less than two grains for an adult.

HENRY F. SEMPLE, M.R.C.S., L.R.C.P.Lond.

Budleigh Salterton.

FATAL HÆMORRHAGE FROM THE INTERNAL SAPHENOUS VEIN.

A. G., aged 23, a laundress, single, was walking home on June 20th, about 8 P.M., when another girl with her noticed blood on the pavement evidently coming from A. G. She pointed this out to A. G., and they hurried along to get home, but, after going nearly 400 yards, she was unable to go any further, and fell down in a fainting condition. She was lifted on to a hand-cart and taken home, but found to be dead on arriving there. A *post-mortem* examination made thirty-six hours after death showed extreme blanching of the body, there being hardly any *post-mortem* stasis visible. Rigor mortis was well marked. On both legs, just below the knee, was a circular mark the result of tight garters; on the inner side of the left leg were three superficial ulcers about the size of half-crowns; on the inner and posterior surface of the right leg were five ulcers. One of these, measuring about one inch and a half by one inch, situated on the inner surface of the leg about four inches below the knee, had extended into the internal saphenous vein, there being a circular orifice through which a probe could be easily passed. The superficial veins of both legs were very varicose. The viscera were all very pale. The points of interest in this case are the pernicious effect of wearing garters below the knee, especially in occupations involving long periods of standing, and the rapidity with which fatal hæmorrhage ensues, which is said to be due to the destruction of the valves in varicose veins, and which was probably increased by attempts to raise the patient after Nature had attempted to arrest the hæmorrhage by producing a fainting condition.

Kingston-on-Thames.

ROBERT CAPES, M.R.C.S.

HEREDITARY TUFT OF WHITE HAIR IN THE FOREHEAD.
ISOLATED cases of congenital canities are far from uncommon, but the instances in which this occurs as an hereditary trait are very unusual. A boy, aged 13, lately came under my care with lupus of the nostrils, for whom I performed Rouge's operation of exposing the nares by detaching and raising his upper lip. He was the possessor of a small tuft of perfectly white hair, which sprang from the centre of the forehead. It appears that this is hereditary. The mother has an identical patch, so has her father and several of his sisters, and it exists in some of their children. The grandchildren of this boy's mother also exhibit the same peculiarity, so that it can be seen occurring in members of four generations.

A case is related by Riggoli of an Italian family in which a similar tuft of white hair occurred in girls and boys through four generations, although absent in some members of the family.

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JOHN H. MORGAN.