

Insanity and Indicanuria (Indoxyluria): A Note of Criticism. By C. C. EASTERBROOK, M.A., M.D., F.R.C.P.Ed., Medical Superintendent Ayr District Asylum, N.B.

Two papers have recently appeared in the Journal indicating a causal relationship between indoxyluria, alimentary toxæmia, and melancholia. One paper, published by Arthur A. D. Townsend in January, 1905 (*Journal of Mental Science*, 1905, p. 51), is entitled "Mental Depression and Melancholia, considered in regard to Auto-intoxication, with Special Reference to the Presence of Indoxyl in the Urine and its Clinical Significance"; the other paper, published by Lewis C. Bruce in July, 1906 (*Journal of Mental Science*, 1906, p. 501), bears the title "The Clinical Significance of Indoxyl in the Urine."

Dr. Townsend's *method of investigating* this problem is as follows in his own words: "The test that I have used for demonstrating the amount of indoxyl present is that known as Jaffé's. The urine is mixed with an equal quantity of strong hydrochloric acid, by which means indoxyl sulphate is decomposed and indoxyl liberated. A very minute amount of calcium hypochlorite is now added (great care is necessary to avoid excess), oxidation of the indoxyl takes place, and indigo blue is formed. The mixture is then shaken up with chloroform, which takes up the indigo blue, the depth of colour indicating the amount of indoxyl present. The colour reaction in normal urine is very slight, the faintest tinge of blue; frequently it cannot be obtained. I have always used Jaffé's test, as by keeping to one method uniformity of result is more easily obtained. To indicate the amount of indoxyl present I use the terms (1) faint trace, (2) moderate excess, (3) large excess—No. (1) a faint blue colour, as appears in the most normal urines; No. (2) a brilliant bright blue colour; No. (3) a very deep blue, in some cases almost approaching to black."

Dr. Townsend's *conclusions*, based on observations by this method in sixteen cases of melancholia and thirteen cases of mania admitted into Barnwood House, are as follows: "So far as my investigations have been carried they have, briefly to recapitulate, enabled me to make the following deductions: 1st, that in depressed states indoxyl is excreted in excess; 2nd, that patients excreting indoxyl in excess exhibit symptoms and

signs of toxæmia; 3rd, that in states of mental elation there is seldom any increase, the amount excreted being normal or less than normal; 4th, that in some states of mental alternation indoxyl is excreted in excess during both melancholic and maniacal phases; 5th, that the more severe the mental attack the greater the excess of indoxyl; 6th, the greater the excess of indoxyl the more marked are the symptoms and signs of toxæmia; 7th, that mental recovery was in the cases I record preceded by the reduction to normal of the amount of indoxyl excreted."

And Dr. Townsend finally concludes: "So far as my observations have been carried they have enabled me to show that indoxyl is found in excess in the urine of patients suffering from acute melancholia; it therefore follows that we have in the intestinal tract of these cases a condition favourable to the formation of toxins. In the brief record of the various cases I have pointed out those signs and symptoms suggesting the absorption of these toxins and the establishment of the state of toxæmia. Whether, however, the putrefactive processes associated with these mental states are primary and causative, or whether they are but secondary and complicating, future investigations must decide."

Dr. Bruce describes the *method*—a modification of Jaffé's—employed by him as follows: "One-third of a test-tube of urine is treated with an equal quantity of strong hydrochloric acid, 1-2 c.c. of chloroform and a drop of a one-half saturated solution of calcium chloride. The test-tube is corked and repeatedly inverted, when the chloroform takes up the indigo and falls to the bottom of the test-tube. Instead of calcium chloride solution very small quantities of calcium hypochlorite may be used instead. Great care has to be taken on adding the oxidising agent that too large a quantity is not used, as an excess of the oxidising agent discharges the colour. Instead of calcium chloride solution or bleaching powder, a 2 *per cent.* solution of potassium permanganate may be employed as the oxidising agent. I have never got satisfactory results when using potassium permanganate. When indoxyl is present in excess in the urine the chloroform becomes dark blue, or even black; when it is absent the chloroform is colourless. Between these two conditions there exists every shade of colour. Judging from the results of testing the urines of persons in

health, I am of opinion that any shade of blue over medium or cobalt colour is a pathological excess."

Dr. Bruce's *conclusions*, based on observations by this method in twenty-seven cases admitted into Perth District Asylum, are as follows: "As the result of these observations I conclude (1) that there is some connection between this symptom of the presence of excess of indoxyl in the urine and the mental symptom of depression; (2) that, to judge by the result of treatment in one of the cases, the indoxyl may have been the chief causative factor in the mental disease; (3) the evidence is in favour of the indoxyl being the cause of the depression rather than the depression being the cause of the presence of the indoxyl; (4) the fact that four typical cases of melancholia had no indoxyl in the urine appears to be evidence that we cannot regard all cases of melancholia as suffering from indoxyl poisoning; (5) that the presence of an excess of indoxyl in the urine means a loaded alimentary tract, which should at once be treated by the use of large enemata—two or three pints of normal saline solution by preference—and the placing of the patient on a purely milk dietary or a milk and farinaceous dietary."

Dr. Townsend, in short, being struck by the frequency of excessive indoxyluria in his cases of melancholia, concludes that in these cases the intestine is in a condition favourable to the formation of toxins and the establishment of toxæmia, and that the toxins so formed may be the primary causative factor of melancholia. He, however, states in an earlier part of his paper: "I may here remark that all the cases that I have examined came under my care after the mental symptoms were fully established, and thus I have not had the opportunity to observe whether the putrefactive process preceded or followed the mental symptoms; any opinion that I have formed regarding this most important question is the outcome of my observations during the progress of the cases."

Dr. Bruce boldly asserts that the toxin in question is indoxyl itself. "I take for granted that there is no question as to the existence of the substance indoxyl or to the fact that it is a toxic substance," he says, and he practically concludes that most cases of melancholia are cases of indoxyl poisoning.

Are the conclusions of these two observers to be accepted? Are their observations in accordance with one's own ex-

perience? Are they sufficiently comprehensive? Are their methods of investigation, which for clearness of discussion have been quoted in full in their own words, sufficiently reliable and free from fallacy?

The indican (potassium indoxyl sulphate) of normal urine is derived from the indol in the intestine. The indol in the intestine is derived from the decomposition of the proteids of the food by the putrefactive bacteria which normally inhabit the alimentary tract. This bacterial putrefaction of the proteids of the food is in health practically confined to the large intestine; and the extent of the process is determined by three factors, namely the amount of proteid supplied in the food, the length of time the fæces are retained in the intestine, and the number and activity of the putrefactive bacteria present in the intestine, and, as B. Moore (Schäfer's *Text-Book of Physiology*, vol. i, p. 464) has pointed out, is gauged more accurately by the amount of decomposition products formed than by the frequency of the bacteria, which, though present, may not be active. The first and second factors above mentioned are controllable, and in investigations on the amount of indican in the urine they must be controlled in order to insure accuracy, for an increase of proteid in the food and especially the occurrence of constipation will materially augment the indican in the urine. The latter observation was first emphasized by v. Jaksch, who states that "a very conspicuous degree of indicanuria may result from simple constipation" (*Clinical Diagnosis*, 5th ed. by Garrod, p. 386), and has since been confirmed by physiologists and physicians generally; and I may add that in my experience it is very common to meet with a marked indican reaction in the urine of patients newly admitted to hospital or asylum, and to find that this marked reaction disappears after free evacuation of the bowel by means of calomel and magnesium sulphate or other means. For these reasons no pathological significance is to be attached to a marked indican reaction in the urine of new patients who are so frequently admitted into hospitals or asylums with a loaded bowel containing one does not know how much decomposing proteid, and until the factors of the indoxyluria of simple constipation and excessive animal diet have been eliminated, one is not justified in regarding the phenomenon observed as pathological. It is necessary therefore in observations on the amount of

indican in the urine in the first place to fix the amount of proteid in the food and secure the regular daily action of the bowel. This is most satisfactorily done by confining the patient to bed during the period of observation, putting him on a fixed mixed diet containing proteids in moderate amount, and securing at least one alvine evacuation daily by means of a sufficiency of fresh vegetables or fruit in the diet prescribed or by the use of simple aperients or simple enemata if necessary. With the patient brought thus into a condition of what may be called intestinal equilibrium, the persistence of an excess of indican in the urine would be pathological. Such indicanuria, however, would not necessarily signify excessive proteid putrefaction in the intestine; for indicanuria may arise from proteid putrefactions elsewhere in the body—for example, fœtid suppurations, putrid phthisis, or gangrene of lungs—which factors must therefore be eliminated before coming to a diagnosis of morbid intestinal putrefaction. If, however, the latter condition is suspected, and if the observations on the amount of indican in the urine are to be taken as a measure of the intestinal proteid putrefaction, control observations should be made of the fæces, in which the parent substance, the indol of the gut, is largely removed. The degree of fœtor and flatus of the stools roughly indicates the extent to which intestinal putrefactions are going on. The indol and closely allied skatol (methyl indol) of proteid origin give to normal fæces their characteristic unpleasant putrescent or “fæcal” odour; they are separable from the fæces by distillation and are soluble in water, and addition of fuming nitric acid to their aqueous solutions gives a red colour (indigo red) with indol and a milky turbidity with skatol. Besides this indol and skatol, the fæces contain volatile fatty acids, ammonia, and the intestinal gases (marsh gas, sulphuretted hydrogen, hydrogen, nitrogen and carbonic acid), all of which are bacterial decomposition products of the proteids, carbohydrates, and fats of the food in health. Adolf Schmidt has shown that an estimation of these gaseous fermentations can be made, on a fixed diet, by incubating for twenty-four hours five grammes of the fæces placed in a Strasburgher’s fermentation tube. The gases formed cause the water to rise in an indicator tube to a height proportional to the activity of the fermentation; and further, if the gases have a putrid odour and the fæces are alkaline, the fermentation

is mainly proteid, whereas the rancid odour of butyric acid and an acid reaction indicate a fermentation mainly of carbohydrates.

Given, then, a daily fixed supply of proteid in the food, given a daily action of the bowel, and given controlling daily observations at least of the degree of foetor and flatus of the stools, the observations on the urine itself, in a metabolic inquiry of this nature, must likewise be daily and continuous, maintained for a week at a time at least, and repeated subsequently on similar lines; and obviously the urine of twenty-four hours must be collected daily during the period of observation, and the amount of indican in each day's urine estimated by a reliable process. The only precise method of estimation is a quantitative one, such as Salkowski's colorimetric process. Jaffé's test is, properly speaking, a process for the detection rather than the estimation of the indican; and, further, it is subject to fallacy if albumen is present in the urine, for Halliburton has shown that strong hydrochloric acid gives a blue colour with albumen, which therefore, if present, must be removed before the test is applied. If, however, the amount of indican is to be gauged by the depth of blue yielded by Jaffé's test, it is not only advisable to have a series of standard tints of indigo blue solution for comparison, but it is also necessary to insure that a fair comparison is being made between the various samples of urine examined. For example, suppose that two patients happen to be excreting in the urine the same amount of indican, and that one patient passes 30 oz. of urine in the twenty-four hours and the other 60 oz. The former urine, containing a more concentrated solution of indican, will obviously give a darker coloration than the latter, and the wrong inference might be made that the former patient was secreting more indican. It is clear, therefore, that if the amount of indican in the urine is to be gauged by the depth of tint produced, the total daily urine must, by dilution or concentration, be brought to a standard bulk (say, of 60 oz.) before the test is applied. No reference is made by Dr. Townsend or Dr. Bruce in their two papers to the adoption of any of the precautions above described, and to my mind necessary in an investigation of this kind.

In examining a specimen of urine it has been my invariable practice, after noting its physical characters and reaction, to

begin the chemical analysis with the following test: About 10 c.c. of urine are heated to boiling point in a test-tube, and pure nitric acid is then added gently drop by drop down the side of the tube. This simple test, which is sufficiently accurate for ordinary clinical purposes, gives positive information as to the presence in the sample of urine examined of (1) an excess of urates, (2) an excess of phosphates, (3) an excess of chromogens, (4) bile, and (5) albumen (confirmed in doubtful cases by the picric acid test). The excess of chromogens is indicated by a violet or red colour, or a mixture of these, this coloration being due to the oxidation of the potassium indoxyl sulphate (indican) to indigo blue, and especially to its isomer indigo red. The first drop of nitric acid often gives the violet colour, and with succeeding drops the colour usually becomes red, and as drop by drop is added the red colour gradually reaches a maximum intensity and then begins to fade, and finally disappears. Nitric acid, in short, as acid decomposes the indican and liberates indoxyl, and as oxidising agent oxidises the latter to the red isomer of indigo chiefly; and as soon as all the indoxyl has been thus oxidised any excess of nitric acid added begins to oxidise the indigo red itself, and so discharges it. If excess of nitric acid is added at the start, any indigo red formed is at once decolorised, and so may escape detection. The above test is simpler than Jaffé's, and gives equally reliable information about the indican present in the sample. In many cases I have carried out both tests with the same urine, and found the results of the examination identical, the same urine giving with both tests either a faint reaction, or a moderate reaction, or a marked reaction as the case may be. Gowland Hopkins states that indigo red and indigo blue have the same physiological significance, and, quoting Rosin, points out that indigo red is more apt to form than indigo blue if heat is employed in carrying out Jaffé's test, cold favouring the appearance of the blue isomer and heat favouring the red. This probably explains the predominant formation of indigo red in the test above described. In applying the above test a faint turbidity sometimes appears, not after boiling the urine (and therefore not due to the presence of albumen or an excess of phosphates), but on the addition of the nitric acid, and possibly this is due to a higher oxidation product of potassium skatoxyl sulphate, which has the same significance in the urine as

indican. Some observers, following Brieger, state that there is a "skatol red" corresponding to indigo red, but Gowland Hopkins says that a "skatol red" is never obtained from human urine, and in a private communication he tells me that there is now no proof of a skatol (as distinguished from an indol) derivative appearing in the urine at all. Both in Jaffé's test and in the test above described a reddish colour may appear, due to urorosein, but addition of chloroform on cooling the urine takes up the indigo red, but not the urorosein, and so serves to distinguish the two substances. The constitution and significance of urorosein are unknown, but it is thought by some to be of intestinal origin also.

During the past fourteen years I have examined with the above test the urines of approximately 500 "fever" cases, 500 ordinary "medical" and "surgical" cases, and 2000 "mental" cases, at the time of admission of these patients into hospital or asylum. As before mentioned, I frequently obtained a marked indican reaction in the urine of these patients which disappeared after the action of calomel and magnesium sulphate or other aperients, or enemata, and therefore probably signified nothing more than constipation, with its attendant excessive putrefaction. The indicanuria was often marked in the fever patients, and specially so in typhoid cases admitted with meteorism and a loaded bowel. Amongst ordinary hospital cases the indicanuria was met with in a great variety of conditions, and seemed to have no significance apart from that of constipation. Similarly amongst asylum cases on admission I have obtained a marked indican reaction in many varieties of insanity, including melancholia, mania, delusional insanity, stupor, dementia, congenital insanity, alcoholic insanity proper, and general paralysis. Many of these patients after an interval of asylum residence, owing to the failure of general therapeutic measures, were given special treatment with animal extracts and other remedies, during the carrying out of which I made special observations of the apparent effect of these remedies on the metabolism of the patient. The patients were consequently confined to bed, and put on a fixed mixed diet, and the action of the bowels, the amount of sleep, and other functions were regulated as carefully as possible, so as to bring about metabolic equilibrium before a commencement was made with the administration of the drugs in

question. Periodic observations were made on the urine, and in many cases daily estimations of the total solids, urea, and phosphoric acid excreted, and an excessive indican reaction if present was always noted. In the great majority of the cases, probably owing to regulation of the bowels prior to confinement to bed for this special treatment, there was no excessive indican reaction. In some cases of thyroid treatment, with large doses of the dried and compressed gland tissue, indigo red and uroscopin reactions were increased during the administrations, possibly owing to the extra proteid supply. The only cases in which indicanuria persisted amongst the patients whom I had under special observation in this way were certain cases of general paralysis, exhibiting marked mental confusion and resistiveness, and other confused and stuporose patients who also exhibited marked passivity, immobility, and resistiveness, and a certain amount of emotional depression. In these cases there was a tendency to marked constipation or to diarrhoea, with loose foetid stools. Various so-called intestinal antiseptic remedies were tried in these cases, but without avail, and in those which ended fatally, both the general paralytics and the stuporose patients, distinct catarrh of the intestine with atrophic changes was found *post mortem*. In these cases there was distinct evidence of excessive intestinal putrefactions, and probably an accompanying toxæmia from the bowel; but in the earlier stages of these cases intestinal symptoms were not present, and there was no history of gastric or intestinal derangement prior to the onset of the general paralysis or stupor.

A perusal of Dr. Townsend's cases shows that in all his cases of melancholia except one (No. 16), in which, however, the motions are described as very offensive, the bowels were constipated and usually "very costive"; and this suggests that the indoxyluria observed was attributable to constipation. A perusal of Dr. Bruce's cases similarly suggests that the indicanuria observed was associated with and explained by constipation; and naturally the indican in the urine in his cases was not only reduced, but apparently temporarily dispelled by his effective method of emptying the large bowel by means of copious enemata. The indoxyluria met with in their cases seems to me, therefore, to have no significance in melancholia apart from the constipation which is so frequently met with in

melancholia, and so frequently calls for special treatment. The question therefore arises, Does constipation more commonly precede or more commonly follow the onset of melancholia? In my experience the proportion of cases in which there is obtained a definite history of constipation prior to the onset of melancholia is very much smaller than the proportion of cases in which the constipation sets in after the melancholia has commenced; and the frequency of constipation in the course of melancholia is readily explainable by a passivity of the visceral musculature, comparable to the passivity of the voluntary musculature which is so characteristic a feature in typical melancholia, though insufficiently recognised, and probably means diminution of efferent outflow from the depressed higher nerve-centres. In conditions of stupor and katatonia, which are often evolved out of melancholia, this passivity of the musculature is more marked, and may amount to immobile resistive, cataleptic, or even paretic, conditions of the muscles and in such states there is a great tendency to constipation with resultant indicanuria. The sequence of events, therefore, in my experience is melancholia, constipation, indoxyluria. The indoxyluria is an adventitious symptom, and signifies constipation, both of which may be dispelled by proper remedies, and still the melancholia continues. The occurrence of indoxyluria signifies constipation, and therefore excessive putrefaction of proteid matter in the bowel, and therefore quite probably the formation and absorption of toxic substances from the bowel—that is, auto-intoxication or toxæmia—but the occurrence of indoxyluria does not signify that melancholia itself is toxæmic in origin or nature; and indoxyl itself as formed in the body is not regarded by physiologists, so far as I am aware, as a toxic substance. The indol and skatol of the gut, though useless, are probably harmless. The same possibly cannot be said of certain other aromatic bodies, as phenol, cresol, and aromatic oxy-acids which are similarly derived from the putrefaction of proteids in the intestines in health, and, like the absorbed portion of the indol and skatol, are similarly excreted in the urine (and in traces in the sweat) as stable “conjugated,” or “ethereal” sulphates, which can be estimated quantitatively as by the Baumann-Salkowski method. The estimation of the total ethereal sulphates in the urine rather than of the potassium indoxyl sulphate alone would, therefore, give a more reliable

indication of the extent, and possible toxic significance, of the bacterial putrefaction of proteids which normally occurs in the intestine.

Recent Medico-Legal Cases.

REPORTED BY DR. MERCIER.

[The Editors request that members will oblige by sending full newspaper reports of all cases of interest as published by the local press at the time of the assizes.]

THE TOWNSHEND CASE.

THIS was an inquisition held to determine the competence of the Marquis Townshend to manage himself and his affairs. It was held before Mr. Justice Bucknill and a jury, and lasted ten days. It attracted a great deal of notoriety in consequence of the introduction of various side issues into the case. The history of the case is long and complicated. The Marquis, now a man of thirty-nine years of age, had been estranged from his family, and had been living in the house, and much under the influence, of a clergyman named Robins. By the influence of a clerk in Somerset House named Dunne, and a woman of title, a Lady Fawcett, who bargained to receive commissions for their services, the Marquis was introduced to a Mr. Sutherst, who was at the same time a barrister and an undischarged bankrupt, but who lived in an expensive way and was believed to be a wealthy man. The object of the introduction was the marriage of Lord Townshend to Miss Sutherst, and after various negotiations, of which Lord Townshend was ignorant, the marriage duly took place. It was not long before differences arose in this strangely constituted family. The Marquis found that Mr. and Mrs. Sutherst assumed, as he thought, an undue authority in his household. They invited to his table persons to whom he objected, and, on his making his objections known, his mother-in-law slapped his face. There was another source of difference between the Marquis and the Marchioness of a graver character. The Marquis's position became so intolerable that he left the house and rejoined his old friend Mr. Robins, who lived at Brighton. From thence he was induced by the Suthersts to return to the house in London. Dr. Milne Bramwell was consulted, and subsequently Dr. Savage also. They