ON THE
PARTIAL METABOLISM, BY THE LIVER,
OF
LEUCIN AND TYROSIN INTO UREA.

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HAVING been taught to regard the presence of leucin and tyrosin in the urine as diagnostic of that exceedingly rare disease of the liver known as acute yellow atrophy, or when occurring in typhus, smallpox, and some of the other exanthemata, as only indicating concurrent acute atrophy of the liver, I, on finding that the urine of a patient under my charge (No. 1 in the list quoted in the following pages) evidenced the presence of leucin and tyrosin, became alarmed for his safety, and it caused me, on the first occasion presenting, to seek the advice and assistance of a Newcastle physician.

The fact that not only did my patient recover, and his urine cease, for the time being, to produce, on analysis, leucin and tyrosin, but that they returned in greater or less

amount with each return of his former symptoms, caused me to look for leucin and tyrosin in the urine of other patients; first, in those similarly situated with respect to their ailments, and, finally, under every form or modification of disease likely to result in interruption of the hepatic functions. The result of my investigations is, that leucin and tyrosin are found in the urine under numerous different pathological conditions, whether affecting the liver intrinsically or from without; and that as often and as soon as the patient recovers, these substitution-products for urea, as they are termed, first diminish in amount, and finally, in most instances, disappear. The numbers, quoted and recorded in the following pages (33), represent individuals, not cases, for some of the patients returned under treatment after a longer or shorter interval on several occasions; so that, counted as cases, they would amount to more than sixty.

Method of preparation of leucin and tyrosin.—The method adopted for preparing leucin and tyrosin has usually been the following:—To four fluid ounces of urine add of a standard solution of lead acetate an excess, so that, on filtering a small quantity of the mixture, and adding thereto a drop of the lead acetate solution, no precipitate occurs. Filter. H_2S is then passed through to throw down the excess of lead. Again filter, and gently evaporate the filtrate in a water-bath to the consistency of syrup. Set aside for a day or two, for the tyrosin, if present, to crystallize out. Pour off and evaporate to dryness. Extract the residue with boiling alcohol. Filter. Evaporate the filtrate to a syrup. If required to purify (the leucin) still further, Hoppe-Seyler's method is applied, viz.:—Dissolve in ammonia, add lead acetate till no further precipitate is produced. Filter. Wash the precipitate with a little water. Suspend it in water, and pass H_2S through it. Filter. Evaporate the filtrate in the water-bath.

Test for leucin.—The smell of amylamine.

Tests for leucin and tyrosin:

Scherer's test for leucin and tyrosin.

Hoffmann's test for tyrosin.

Piria's test for tyrosin.

Microscopic test for both.

Over 500 analyses for leucin and tyrosin have been made by me within the past two years.

Many authorities might be quoted in support of the statement that the almost universal consensus of opinion is to the effect that "the presence in the urine of leucin and tyrosin exists most especially in that very rare disease known as acute yellow atrophy, that they are only occasionally present in some few other diseases, viz. in chronic yellow atrophy and leucocythemia (Beale); in typhus, smallpox, and other exanthemata (Frerichs and Städeler); attributed, however, to the probable concurrence of yellow atrophy (Murchison); and only one to 'remora' or hindrance to the hepatic circulation, due to valvular disease of the heart (Balfour)."

I proceed to give a list of patients suffering from a variety of complaints, in the course of which either leucin alone, or it in company with tyrosin and uric acid, was present in the urine.

No. 1. W. R—, first seen on November 11th, 1877. Jaundice.

Nov. 25th. *Urinary examination*.—Leucin and tyrosin present in large amount. Met Dr. G. H. Philipson, of Newcastle, in consultation, to whom I showed the mounted microscopic slides of leucin and tyrosin.

Result.—Recovery. All but traces of leucin and tyrosin in time disappeared. Occasionally, since then, leucin has reappeared, to again disappear under administration of hepatic stimulants, and notably of euonymin.

No. 2. Ann D—, æt. about 56; a stout, dark-complexioned woman. Heart: area of dulness increased, with mitral systolic and aortic systolic bruits.

Jan. 12th, 1878. *Urinary examination*.—Leucin present. Under treatment she improved, although leucin is, more or less, constantly present.

No. 3. D. McVai, æt. 35; first seen on January 19th, 1878. For years had been a hard beer and spirit drinker. Spleen: area of dulness increased. Liver small, contracted. Skin dry, anasarcaous. Abdomen tympanitic, ascitic.

Urinary examination.—Acid, no albumin, bile, sugar; leucin and tyrosin in very large amount. He entered Durham Infirmary as an in-patient on the same day, and was discharged at the end of a few weeks. He died, I am informed, in September, 1878. I saw him once in the interim after his return from Durham, and examined again his urine, which still contained leucin and tyrosin in considerable amount. Cause of death stated to be English cholera: most probably from the form of diarrhoea consequent upon the advanced stage of his disease—cirrhosis.

No. 4. R—, an overman in a coal mine; February, 1878. Complained of giddiness, loss of appetite, &c. Liver: area of dulness increased, sluggish.

Urinary examination.—Bile, sugar, leucin.

Result.—Recovery; leucin disappeared.

No. 5. R. D—, a coalheaver, æt. 23; February, 1878. Suffering from rheumatic fever and hypostatic pneumonia. Pericardium so full of fluid as to almost completely mask the sounds of the heart. Liver: area of dulness increased and very inactive.

Urinary examination. March 17th, 1878.—Leucin in large quantity.

March 25th.—Mere trace of leucin.

Result.—Recovery with, on absorption of pericardial fluid, evidence of mitral insufficiency. Occasionally leucin reappeared.

No. 6. J. G—, æt. 32; February, 1878. Suffering from pneumonia and acute rheumatism.

Urinary examination.—Leucin.

Result.—Recovery, with disappearance of leucin.

No. 7. W. P—, an overman, æt. 44. Suffering from

dyspepsia, with alternations of the uric acid and oxalic acid diatheses. Occasionally suffered from acute nephritis, and some months ago passed a calculus per urethram.

Urinary examination.—Albumin, pus, mucus, uric acid, and leucin.

Result.—After passage of calculus, recovery.

No. 8. J. A—, coke drawer, æt. 19½. January, 1878. Complained of headache, giddiness, anorexia, and loss of strength. He was excessively anæmic. Liver: area increased, tender, sluggish. Spleen area increased.

Urinary examination.—Leucin.

Treatment.—Ferruginous tonics, hepatic stimulants, gentle alvine evacuants, and generous, easily digestible, unstimulating diet. To cease smoking.

Result.—Returned to work in about six weeks. Leucin disappeared.

No. 9. J. W—, a putter, æt. 14. First seen August 19th, 1878. The subject of phthisis, and of intestinal obstruction, caused, most probably, by one or more bands of organisable lymph.

Urinary examination.—Leucin and tyrosin in very large amount.

Result.—Death.

No. 10. J. H—, a publican. First seen July 29th, 1878. Suffering from colic. (The subject, in September, 1877, of fæcal obstruction accompanied with jaundice, and of the presence in urine of bile and albumen.)

Urinary examination.—Leucin and tyrosin in very large amount.

Result.—Recovery, with complete temporary disappearance, first of tyrosin, and then of leucin. Occasionally leucin has reappeared.

No. 11. W—, a coal hewer. August 6th, 1878. Suffering from right pleuro-pneumonia.

Urinary examination.—Leucin and tyrosin in very large amount.

Result.—Recovery.

No. 12. Miss G—, æt. 40. The subject of bronchitis, with great exacerbation, especially if liver sluggish.

Sept. 5th, 1878. *Urinary examination*.—Leucin and tyrosin in large amount. Temperature 103·5° F. Salicylic acid administered; within less than twenty-four hours temperature reduced to 98·6° F., with relief of all symptoms, and increased quantity of urine, which, upon analysis, showed great diminution of leucin and tyrosin, and increased quantity of urea.

This patient takes now, regularly from one and a half to three grains of euonymin, and keeps by her a mixture containing salicylic acid; and although, for years past, a great sufferer from bronchitis, she has for months been nearly free.

No. 13. Mrs. H—, a short stout woman. Suffering from frequent hepatic derangement.

Oct. 13th, 1878. *Urinary examination*.—Leucin in large quantity, to disappear on recovery, and reappear in each successive attack.

No. 14. Mrs. H—, October 22nd, 1878. Suffering from varicose ulcer of the leg, and much inaction of the liver.

Urinary examination.—Leucin in large amount.

No. 15. Mrs. H. R—. Has occasional severe attacks of hepatic derangement.

Oct. 22nd, 1878. *Urinary examination*.—Leucin in large amount, tyrosin in smaller quantity.

Result.—Recovery; both disappeared.

No. 16. T. J—, æt. 66; an active free-living man, with heart displacement to right, intermittent pulse, and emphysema of left lung.

Urinary examination.—Leucin.

No. 17. A female patient in Stockton-on-Tees Hospital, with Bright's disease, and presystolic and mitral systolic bruits.

Urinary examination. Nov. 12th, 1878.—Inter alia, leucin and tyrosin in large amount. She became better, and worked in the hospital for some months, but finally succumbed to Bright's disease, &c.

No. 18. Mrs. T—, senr., æt. 56. Bronchitis, with occasionally spasmodic asthma.

Urinary examination.—Leucin.

No. 19. John S—, a blacksmith. Rheumatism.

Urinary examination.—Tyrosin in large amount. Leucin in smaller. (He drank freely). Urine several times afterwards examined, with result of disappearance first of tyrosin, and then of leucin.

No. 20. H. D—, senr., æt. 65. Pleuro-pneumonia of right side and base of right lung behind.

Nov. 30th, 1878, *Urinary examination.*—Leucin and tyrosin in very large amount. During returning convalescence tyrosin first disappeared, and lastly leucin.

No. 21. R. D—, an overman. Sudden attack of giddiness. Liver very inactive.

Dec. 12th, 1878. *Urinary examination.*—Leucin.

No. 22. Margaret D—, æt. 20. Puerperal eclampsia on January 31st, 1879.

Urinary examination.—Of about five fluid ounces, the total amount passed in the three first days. Albumin copious; uric acid in excessive quantity; urea very deficient; very large amount of leucin and tyrosin (particularly of the latter, 25, 11, 79).

Result.—Recovery, with total disappearance of leucin and tyrosin, diminution of uric acid, disappearance of albumin, and increase of urea.

No. 23. Miss McC—, Salop. Chronic and spasmodic asthma.

Aug. 14th 1879. *Urinary examination.*—Leucin.

Treatment.—Inter alia, euonymin nightly, and gentle evacuant each succeeding morning.

28th.—Considerably improved in health. Leucin reduced in quantity.

No. 24. Thomas A—, Salop. Incipient delirium tremens after much drinking.

Aug. 16th, 1879. *Urinary examination*.—Leucin and tyrosin and large amount of albumin.

25th.—No albumin, but leucin still present. Tyrosin disappeared. Himself well and about.

No. 25. Miss M—, Salop. Phthisis.

Aug. 19th, 1879. *Urinary examination*.—Leucin in large amount.

No. 26. Miss K—, Salop; æt. 24. Chronic asthma with spasmodic attacks.

Aug. 23rd, 1879. *Urinary examination*.—Leucin in very large amount.

No. 27. John M—, Salop. Labourer; a somewhat free drinker. Left lung somewhat emphysematous; heart displaced to right; area of liver increased.

Aug. 25th, 1879. *Urinary examination*.—Leucin.

No. 28. S. T. B. B—, Salop (æt. about 70). Hemiplegia of about four years' standing; about three times epileptic. Liver sluggish. In other respects healthy with vigorous intellect.

Urinary examination. From August 6th to 29th.—Albumin in small quantity. No urinary casts. Leucin.

Result.—Albumin reduced to mere trace; leucin lessened in amount. More urea and more water passed in urine. General health considerably improved.

Treatment.—Euonymin gr. ij or gr. iss nightly, with from fluid ℥iv to fluid ℥viij of Friedrichshall every succeeding morning. Most other medicine discontinued.

No. 29. K. W—, æt. 32. Chronic asthma.

Aug. 30th, 1879. *Urinary examination*.—Leucin and tyrosin.

No. 30. M. W—, æt. 5. Infantile jaundice. A strong, active, healthy child, apparently.

Aug. 30th, 1879. *Urinary examination*.—Leucin.

No. 31. Florence W—, Salop, æt. 7. Pertussis.

Sept. 2nd, 1879. *Urinary examination*.—Leucin ; tyrosin in minute amount (25, 11, 79).

No. 32. Old female patient in Stockton-on-Tees Hospital. Jaundice, arising probably from cancer of liver.

Nov. 5th, 1879. *Urinary examination*.—Much tyrosin and leucin.

No. 33. Mrs. R—, æt. 44. Puerperal septicæmia with embolism into base of right lung.

Feb. 1879. *Urinary examination*.—Leucin and tyrosin. *Result*.—Death.

I have thus shown the presence of leucin and tyrosin in the course of eighteen or nineteen different pathological conditions : different in two respects ; viz. as, first, differing among themselves ; and, secondly, differing, inasmuch as they do not include either acute yellow atrophy, typhus, smallpox, or the other exanthemata. If, therefore, these last-named diseases be added to the foregoing, the number of distinct manifestations of disease in which leucin and tyrosin present themselves, is necessarily still further increased.

Physiologically, the sources of leucin and tyrosin are two-fold ; viz. as a result of digestive proteolysis, and, secondly, of the metabolism of the tissues of the organism. Whether they can be re-elaborated into more complex bodies, and thus regenerated into albumin is unknown, although it is more likely to be the case with tyrosin. Respecting the further decomposition of leucin, it is certain that it can be split up into urea by a decomposition into ammonia, and into a fat, or be oxidised into carbonic acid.

Besides the leucin and tyrosin arising as a result of digestive proteolysis, most of which passes directly to the liver through the portal vein, the spleen may be regarded as a

great source of the leucin and tyrosin (at least of leucin, if not of both), arising from the destructive metamorphosis of the tissues of the body. The spleen is by some regarded as a possible source of urea, from its metabolism of leucin and tyrosin; but when it is considered that the only organ in which urea is found normally, in any amount, is the liver, and that the whole of the splenic blood passes into the vena portæ, and thence to the liver, it may reasonably be inferred that it is the office and function of the liver to convert these substances into urea, or to otherwise dispose of them, and that the spleen is, therefore, only indirectly a source of urea.

I have frequently remarked that tyrosin only occurs in the urine in the severer forms of hepatic interruption, and that it is the first to disappear during convalescence. The greater difficulty with which it is, if at all, converted into urea, and the greater complexity of its molecule, would seem to render it quite conceivable that it is more easily so conjugated as to subserve a higher use in the organism than leucin; while its appearance in the urine, on the other hand, in only the severer forms of disease, evidences considerably greater diminution of hepatic functional activity, so that it, as well as leucin, is excreted.

The experiments of Rutherford, Vignal, and Dodd, reported in the 'British Medical Journal,' for 1878, abundantly prove that with regard to the preparations of salicylic and benzoic acid, irrespective of their passage through the kidneys as salicyluric and hippuric acid, they greatly increase the secretion of bile. So likewise with euonymin. I had long known the effect of salicylic acid in increasing very greatly the urates of the urine, but until then I had not used euonymin. From and since this time, however, I have employed it somewhat extensively, and occasionally in conjunction with the salicylates of potash and of soda. As an instance of the beneficial influence of salicylic acid, not only in reducing temperature and increasing the amount of urea, but also in diminishing the quantity of leucin and tyrosin, Case No. 12 is instructive. Since this patient has regularly taken euonymin, followed each succeeding morning by a

gentle evacuant, she has enjoyed a remarkable improvement in health. As to the effect of euonymin alone in reducing the quantity of albumen present in the urine, increasing the urea and quantity of urine passed, and lessening the amount of leucin, No. 28 may be cited. I have used euonymin, notably in cases of asthma complicated with hepatic derangement and the consequent presence in the urine of leucin and tyrosin, and always with marked benefit, both in relieving the more distressing effects of this complaint, in lessening the quantity of leucin and tyrosin, and in warding off or at least lessening the severity of succeeding attacks. I must not be understood as inferring that euonymin combines with glycin in its tendency to increase the formation of urea, but I presume that by its very decided action in augmenting the secretion and flow of bile, it in this manner greatly conduces to the re-establishment of the normal hepatic functions, by enabling the liver to set free and utilise its glycin.

I have thus shown that leucin and tyrosin are present in the urine of man in the course of numerous diseases, and that their presence is not, as hitherto universally held, confined to a few. While the researches and experiments of physiologists prove conclusively that leucin and tyrosin can be and are (especially leucin) converted into urea, and afford the strongest presumption that it is a function of the liver so to convert them, the numerous records of the appearance and disappearance of these substitution-products, leucin and tyrosin, in the course of the diseases, and of their treatment, strengthen and support, in the fullest possible manner, the doctrine of the urea-forming function of the liver.