

POSTURAL OR ORTHOSTATIC ALBUMINURIA

A CRITICAL SUMMARY OF THE LITERATURE

D. R. HOOKER, M.D.

BALTIMORE

Following Richard Bright's observation, in 1827, of the direct association of albuminuria with pathological changes in the kidneys, the medical profession showed a natural tendency to regard the presence of albumin in the urine as a positive sign of nephritis. It was not long after Bright's discovery, however, that cases began to appear in which examination of the urine showed albumin to be present without any evidences of ill health in the patient and without the fatal outcome commonly associated with nephritis. Such observations have steadily increased in number, so that for some time past there has been an increasing tendency toward the belief that albumin in the urine is not necessarily an indication of serious pathological change in the kidney.

This tendency to regard the presence of albumin as of not very serious moment has led to the adoption of numerous terms to define the condition, such as "functional albuminuria," "albuminuria in the apparently healthy," "intermittent albuminuria," "cyclic albuminuria," "albuminuria of adolescents," "physiological albuminuria," "orthostatic albuminuria," etc. For practical convenience I shall divide the papers to be considered into three groups or periods, the first of which extends roughly up to 1887 and ends with a paper published by Dubreuilh, "A Critical Review of Periodic Intermittent Albuminuria."¹

FIRST PERIOD

Leube² was the first to investigate carefully the urine of presumably healthy men. He studied the urine of 119 soldiers in the morning just after they arose from bed, and found albumin in the urine of 4.2 per cent. The urine of the same soldiers in the afternoon, after several hours of marching, showed albumin in 16 per cent.; thus 12 per cent. of these soldiers had albuminuria subsequent to prolonged exercise. In all of these cases, the amount of albumin was very slight, never exceeding one gram per liter. As a result of these observations, Leube classified all kidneys as impermeable, semipermeable, or permeable, and located the

1. Dubreuilh: *Rev. de m d.*, 1887, vii, 678.

2. Leube: *Virchow's Arch. f. path. Anat.*, 1878, lxxii, 145.

permeability in the glomerulus. Capitan³ found albumin in 44 out of 100 soldiers, and in 38 out of 92 children, all in good health. In a thesis published in 1883, Chateaubourg⁴ gave the results of numerous studies on soldiers and other subjects at different times of the day and under different circumstances. These results are collected in Table 1.

TABLE 1.—RESULTS OF CHATEAUBOURG'S URINARY STUDIES

Cases.		Traces of	Albumin
		Albumin.	Above 0.03 Gm.
		%	Per Liter.
Resting	120	76	41
Muscular fatigue after exercise.....	242	87	66
Mental exertion, school boys, age 16-20...	50	92	77
During digestion	94	82	53
After cold baths.....	53	100	90

The difference in the results obtained by these and subsequent observers may perhaps be explained by the reagents employed; thus, Senator and Posner believe that with sufficiently delicate methods albumin may be found in all normal urines.⁵ But, putting aside such cases as the latter, in which the amount of albumin is exceedingly small, there are unquestionably individuals who without any indication of impairment in their general health present an albuminuria which may be easily diagnosed by the coagulation of the protein in the presence of acid. Such cases have been described variously under the names "albuminuria without renal lesion," "albuminuria in the apparently healthy," "albuminuria of puberty," etc. According to some observers, this is nothing but an exaggeration of a normal condition, while others believe that albuminuria invariably indicates a pathological condition of the kidneys. Johnson,⁶ for instance, believed that it represents a latent nephritis, and Gairdner,⁷ on the other hand, has compared the condition to cardiac murmurs, which persist throughout life without other evidences of disease, or to those cases which show localized pulmonary induration, but which never develop acute symptoms of tuberculosis.

Ultzmann⁸ was among the first to observe albuminuria in the healthy. In 1870 he detected albuminuria in the urine of eight young girls, who were apparently healthy and strong. The specific gravity of the urine was increased, but neither casts nor red blood cells were ever found. The

3. Capitan: Thesis, Paris, 1883 (cited by Dubreuilh).

4. Chateaubourg: Thesis, Paris, 1883 (cited by Dubreuilh).

5. Senator: Deutsch. med. Wchnschr., 1904, xxx, 1833.

6. Johnson: Brit. Med. Jour., 1889, i, 225.

7. Gairdner: Brit. Med. Jour., 1884, i, 369.

8. Ultzmann: Wien. med. Presse, 1870, xi, 81.

sediment frequently showed urates and calcium oxalate crystals. In 1873, in a discussion before the Royal Medical and Chirurgical Society of London, Sir William Gull⁹ stated that "boys when they reach the age of puberty are pale and weak, and the urine is frequently albuminous." The first work of importance, however, on this subject was presented by Moxon¹⁰ in 1878. He noted that in young men of delicate complexion, albumin was often found in the day urine. As a result of this paper, the English journals published numerous articles on periodic albuminuria by Rooke,¹¹ Fergusson,¹² Dukes,¹³ Saundby,¹⁴ Yeo¹⁵ and others. In Germany, there appeared the observations of Edlefsen,¹⁶ of Fürbringer,¹⁷ and of Bull.¹⁸ The last-mentioned observer followed the case of a young physician, who had daily albuminuria lasting over two years. Munn,¹⁹ an insurance examiner in New York, found albuminuria in twenty-four persons of various ages, who were apparently perfectly healthy, and whose urine showed albumin in the afternoon, but was entirely free during the night. Macacci²⁰ emphasized the influence of violent exercise. Kinnicutt²¹ also noted intermittent albuminuria in a young man. The latter observer was not able to determine any periodicity, but the character of the urine, its acidity, specific gravity, and the presence of calcium oxalate crystals makes it closely analogous to the type of periodic intermittent albuminuria. The above papers have been collected in a résumé by Lepine, published in the *Revue de médecine*, in 1882. In 1884 Rendall²² published a thesis in which many observations were given to show that albuminuria was intimately connected with the digestive processes. Pavy, on the contrary, at the meeting of the British Medical Association at Cardiff in 1885,²³ insisted on the importance of the upright position, and excluded entirely the influence of digestion. Pavy's position has subsequently been completely justified.²⁴ Teissier, in a paper read before

9. Gull: Brit. Med. Jour., 1873, i, 675.

10. Moxon: Guy's Hosp. Rep., 1878, xxiii, 233.

11. Rooke: Brit. Med. Jour., 1878, ii, 596.

12. Fergusson: Brit. Med. Jour., 1878, ii, 627.

13. Dukes: Brit. Med. Jour., 1878, ii, 794.

14. Saundby: Brit. Med. Jour., 1879, i, 699.

15. Yeo: Brit. Med. Jour., 1878, ii, 627.

16. Edlefsen: Mitth. f. d. Ver. Schleswig-Holsteiner Aerzte, 1879, viii, 21.

17. Fürbringer: Ztschr. f. klin. Med., 1880, i, 340.

18. Bull: Berl. klin. Wehnschr., 1886, xxiii, 717.

19. Munn: Med. Rec., 1879, i, 297.

20. Macacci (cited by Dubreuilh).

21. Kinnicutt: Arch. Med., 1882, vii, 58.

22. Rendall: Thesis, Paris, 1883.

23. Pavy: Lancet, London, 1886, i, 437.

24. Sollmann and McComb: Jour. Exper. Med., 1898, iii, 137. Mendel and Hooker: Jour. Exper. Med., 1901, v, 647.

the National Society of Medicine at Lyons in the same year,²⁵ believed that he was able to show that such albuminuria is nothing but the result of abnormal metabolic processes, resulting from general nutritional disturbances.

This albuminuria may be present without nephritis, and in people without serious disease, and under various circumstances. It is possible, therefore, according to Dubreuilh, to distinguish three types: 1, transitory albuminuria, acute or accidental; 2, chronic albuminuria, without any distinct periodicity; 3, periodic intermittent albuminuria, the cyclic albuminuria of Pavy. The third type is the one which particularly interests us.

ETIOLOGY

Sex plays an important part. Thus, in fifty-five cases observed by Dubreuilh, forty-nine occurred in men and six in women. The age is also important. It is most frequently seen during adolescence and in young adults. In 34 cases studied by Dubreuilh, there were 4 boys and 3 girls under 15 years; 14 boys and 2 girls between 16 and 20 years; 7 men between 20 and 25 years; 6 men between 26 and 30 years, and 3 men above 30 years. The age limit cannot be strictly defined, but it is evident from these figures that it is more common about the twenty-first year.

According to the observations of Moxon, functional albuminuria is often present in several members of the same family. He cites several cases of this kind. They generally present the following characteristics:

The subject is listless, and toward evening, he perhaps takes himself to a couch in a languid way. He complains of a headache, and he looks very anemic and gray and sunken about the eyes. He sleep too much and arises unrefreshed, and is too ready for rest during the working hours. He is usually little disposed to avail himself of cheerful company, but is apt to be content with his state in all these rather unsatisfactory particulars.

According to Teissier, periodic albuminuria is frequently observed in the children of gouty and rheumatic parents, and they are themselves liable to a gouty tendency.

URINARY SYMPTOMS

The amount of urine secreted is usually a little less than normal, but in rare cases it may be augmented. The specific gravity is usually equal to, or slightly greater than, normal, and varies generally between 1.020 and 1.030. The color of the urine is normal in the majority of cases. The acidity is generally above normal, and is accompanied by the presence

25. Teissier: *Lyon Méd.*, 1887, liv, 363.

of uric acid and calcium oxalate crystals. Clark²⁶ believes that there is an association between the albumin and the oxalate crystals, and he has found that if the cases are treated for oxaluria, the albumin will disappear. Jones²⁷ says that Yale medical students used to eat the stalk of common rhubarb in order to secure calcium oxalate crystals for study, which frequently resulted in backache, an irritable bladder and albuminuria. Teissier observed numerous granular plaques having the appearance of spontaneously coagulated albumin. He also noted a delicate, metallic, bluish tint on the surface, and found that the urine showed a striking tendency to adhere to the glass, giving an opalescent appearance to the surface.

The albumin is not very abundant in these cases, never exceeding one gram per liter. The heat-acid test is usually sufficient to show the presence of albumin. According to Jaccoud²⁸ and Maguire,²⁹ the protein present is, in the majority of cases, globulin. The latter observed globulin in three typical cases. Peptone is also occasionally found.

PERIODICITY

This form of albuminuria, the cyclic albuminuria of Pavy, is characterized by both its intermittence and its periodicity. The night urine is practically always free from albumin, while that secreted during the day invariably shows, at one time or another, albumin in considerable amounts. The albumin usually disappears quickly when the subject lies down. Rooke followed the case of a young girl for a long period. He never observed albumin in the urine collected after she lay down. This patient was kept in bed three weeks, during which time albumin never appeared. On the first day, however, that the patient was allowed to get up albumin promptly made its appearance. Pavy reports similar cases, and believes that for each case there is a particular time of day when the albumin is sure to be present. This last observer has never been able to find that food or cold baths have any influence on the appearance of the phenomenon. Rendall and also Dukes, however, reported cases in which food seemed to play a very important part. Such patients, after rest in bed and a milk diet, did not exhibit albuminuria when they were up and about until a mixed diet was allowed, when the albumin promptly made its appearance.

26. Clark: *Brit. Med. Jour.*, 1884, ii, 312.

27. Jones: *Lancet*, London, 1886, i, 432.

28. Jaccoud: *Clin. Méd. de la Pitié*, 1884-85 (cited by Dubreuilh).

29. Maguire: *Lancet*, London, 1886, i, 1106.

Albuminuria in general seems to be very sensitive to cold, although occasionally little or no effect is evident. In some cases, the emotions seem to play an important part; thus Fürbringer, Lépine and Clarke report cases in which emotional excitement has been a predisposing cause. The albuminuria appears each day with the same characteristics. The periodicity may, however, not be a daily occurrence. Thus Rosenbach³⁰ has observed in the case of a generally healthy individual that albuminuria appeared accompanied by headache, loss of appetite, insomnia, etc. The albuminuria in this case lasted from twenty-four to thirty-six hours. The left heart was hypertrophied, and the arterial pressure increased. Teissier has seen the cyclic character of the albuminuria very much altered as the result of exercise. Klemperer³¹ reports the case of a student, 23 years old, who, as the result of a severe indigestion, had albuminuria which cleared up when the digestion returned to normal.

GENERAL SYMPTOMS AND INCIDENTAL DISTURBANCES

These patients usually show no systemic disturbances, although they are, in general, below par in health, as is evident from Moxon's description given above. They are usually described as being of delicate health; they sometimes present the characteristics of a lymphatic temperament, and frequently evidence nervousness. They are usually pale and anemic, and the young girls are often chlorotic. They present sensations of lassitude and marked languor, as emphasized by Gull in 1873, and subsequently by numerous observers. Palpitation of the heart is a frequent symptom, but without hypertrophy, and the pulse is usually soft. Digestive troubles are usually slight, but sometimes dyspepsia is present (Moxon). Vomiting and dilatation of the stomach (Teissier) have been noted. The tongue is often coated and edema of the eyelids, as observed by Fergusson and Dukes, is not uncommon. Languor, headache and coated tongue constitute an important symptomatology, according to the English observers. Teissier has noted the coincidence of disturbances of the skin (erythema, eczema and urticaria). He has also determined, in the albuminuria cycle, the following phases which occur in the course of the day: (1) elimination of an exaggerated amount of coloring matter; (2) albuminuria; (3) elimination of an exaggerated amount of urine; (4) elimination of an exaggerated amount of urea.

Ralfe³² noted the frequent coincidence of simple, chronic albuminuria with paroxysmal hemoglobinuria. Several cases came under his observa-

30. Rosenbach: *Ztschr. f. klin. Med.*, 1883, vi, 240.

31. Klemperer: *Ztschr. f. klin. Med.*, 1887, xii, 177.

32. Ralfe: *Lancet*, London, 1886, ii, 764.

tion which he believed could be intimately associated with the hemoglobinuria. Ralfe, on the basis of the experiments of Noel Paton, believes that the liver is the site of the normal destruction of red blood cells. If, for any reason, this function of the liver is exaggerated under pathological conditions, or as a result of intoxication, the urinary pigments are increased, and if this process goes on far enough, albuminuria results.

According to Ralfe, we have the following schema indicating the relationship between functional albuminuria and hemoglobinuria:

Ordinary hemolysis.	(Urinary pigment, urea.)	Normal urine.
Active hemolysis.	(Increase of urinary pigment, increase of urea.)	Urine of digestion.
Increased hemolysis.	(Increase of urinary pigment, appearance of bile pigment, increase of urea, albumin in urine.)	Functional albuminuria
Extraordinary hemolysis.	(Hemoglobin in urine, increase of urinary and bile pigments, increase of urea, albumin in urine.)	Hemoglobinuria.

It is impossible to determine the duration of the type of albuminuria under discussion. In some cases it lasts a few months, but in others it may continue for two or even eight years. In general, the prognosis is serious, although not necessarily fatal.

Edlefsen is inclined to believe, in accordance with the work of Runeberg,³³ that as a result of exercise, an unusual amount of blood is diverted to the muscular system, which results in a fall of blood-pressure in the kidney, with a consequent albuminuria. Such a mechanical theory, however, fails to account for cases to be mentioned later in which the vertical position with muscular exertion excluded was sufficient to produce an albuminuria and in which muscular exertion in the horizontal position was without effect.

The theory that it is due to digestive disturbances, advanced by Rendall, is unsatisfactory, because it is impossible to find a direct relationship between the appearance of albumin and the time of meals. The effect of cold is, in certain cases, very striking, but it does not apply generally. The same may be said of the idea that emotional states bring about the condition.

SECOND PERIOD

The second period in the development of our subject may be conveniently defined as extending from 1887 until 1904, ending with the

33. Runeberg (*Ztschr. f. physiol. Chem.*, 1882, vi, 508) has shown that protein filters through animal membrane more rapidly with low than with high pressure.

thesis of Guilblain³⁴ in France, and the work of Edel³⁵ in Germany. This second period is characterized by the development of scientific interest, and a strong effort to define the etiology of albuminuria by means other than simple clinical observation. Pavy had suggested the name of "cyclic albuminuria." In 1887 Stirling³⁶ in England proposed the name of "postural," and in 1899 in France, Teissier³⁷ proposed the name "orthostatic albuminuria," which terms more correctly define the phenomenon under discussion.

Postural or orthostatic albuminuria is most likely to occur between the ages of 16 and 22. Thus Dukes³⁸ observed between 200 and 300 cases at Rugby. It was formerly thought that the phenomenon was more frequent in boys than in girls. The more recent work has tended to show, however, that sex is of no importance as an etiological factor. In the majority of cases, occurring as they do at the age of puberty, the albuminuria has been associated with the sex function. Masturbation was known to be practiced by many patients. Thus Stirling³⁹ says that of 37 boys who masturbated, 14 had albuminuria. This author quotes Dickinson as saying, "Most, not all, cases masturbate," and again quotes Dukes, "I do not think masturbation is concerned in it." Stirling is of the opinion that at the age when most cases occur, the sexual functions are rapidly developing, and the nervous mechanism concerned is consequently in an unstable condition. According to Stirling, it is hard to say whether this produces a reflex hyperemia of the kidney, or more probably, a disturbance of the vasomotor system, but he believes that in any case the effect would be much the same. Any cause which would produce this effect might be liable at the same time to produce albuminuria, and therefore albuminuria might be regarded as the result of a local as well as a general deficiency in vascular tone. Dukes and others have suggested that the development of the vascular system at the age of puberty may be an important factor. It is, of course, probable that infectious diseases, such as scarlet fever, which are likely to occur at this time in a child's development, may also play a part. This possibility has led Guilblain to differentiate essential orthostatic albuminuria to cover the cases in which no infections can be found predisposing to the condition. Schaps⁴⁰

34. Guilblain: Thesis, Paris, 1903.

35. Edel: München. med. Wehnschr., 1901, xlviii, 1833; Deutsch. med. Wehnschr., 1903, xxix, 639.

36. Stirling: Brit. Med. Jour., 1887, ii, 1157.

37. Teissier: Semaine Méd., 1899, xix, 425.

38. Dukes: Brit. Med. Jour., 1889, i, 625.

39. Stirling: Brit. Med. Jour., 1889, i, 807.

40. Schaps: Arch. f. Kinderh., 1903, xxxv, 41.

observes that girls are affected four times as commonly as boys, and is inclined to explain this relationship on Rokitansky's observation that developmental anomalies are more common in the vascular system of girls than of boys. Of 35 subjects, 20 showed more or less pathological hearts. These troubles were not, however, organic, but rather due to the hypertrophy and dilatation, coincident to growth described by Germain Sée.

Admitting that posture plays an important part in the causation of albuminuria, numerous observers have sought an explanation in the accompanying muscular exertion. Experimental observation has not, however, confirmed this idea. Thus Guilblain found that muscular exertion in the horizontal position did not cause albumin to appear, and that if the subject was maintained in the upright position passively, albuminuria promptly occurred, and finally, that light exercise tended to decrease rather than to increase the amount of albumin secreted. Osswald⁴¹ also observed that the horizontal position of the body caused the albumin to decrease or disappear in from twenty to sixty minutes. Under such conditions, muscular exertion had no effect on the albuminuria. The same thing was observed when the subject was maintained in the sitting position.

Considerable attention has been paid to the influence of the position of the body on the secretory activity of the kidney. Linossier and Lemoine⁴² studied the amount of water, urea, phosphates and sodium chlorid secreted, standing and lying, in normal individuals, and in those with orthostatic albuminuria. Their results are given in Table 2:

TABLE 2.—RATIO OF VARIOUS SUBSTANCES IN URINE, SUBJECT STANDING AND LYING

	Normal.	Albuminuric.
Water	82:100	64:100
Urea	131:	82:
P ₂ O ₅	112:	80:
NaCl	104:	63:

They are inclined to infer from these figures that orthostatic albuminuria borders on the pathological. Achard⁴³ and Merklen and Claude,⁴⁴ using Koranyi's quotient Δ/NaCl , were unable to find, however, any abnormality in the excretion of urine in subjects with orthostatic albuminuria.

41. Osswald: *Ztschr. f. klin. Med.*, 1894, xxvi, 73.

42. Linossier and Lemoine: *Compt. rend. Soc. de biol.*, 1903, lv, 466.

43. Achard: *Compt. rend. Soc. méd. d. hôp.*, 1900, June 22.

44. Merklen and Claude: *Compt. rend. Soc. méd. d. hôp.*, 1900, July 27.

Blood-pressure has been considered as an important causative factor in albuminuria. Dukes⁴⁵ quotes Benke as saying

The development of the heart at puberty is to be regarded as a very important phase in the development in regard both to the physical and pathological occurrences of this period of life. The large arterial vessels attain their relatively narrowest condition at the time of puberty, hence with the increased development of the heart, with relatively narrow arteries, we must get increased arterial tension.⁴⁶

According to this theory, Dukes presupposed a renal hyperemia, which, in the majority of cases, is just held in check, and believed that he was able to determine increased arterial tension in all of his cases. Craig,⁴⁷ in England, seems to have been the first to suggest definitely that albuminuria is present as the result of low arterial tension; he cites cases of anemia and hemorrhage in which albuminuria is likely to be present. Furthermore, he states that he was able to cause functional albuminuria to disappear by raising the blood-pressure. Herringham⁴⁸ describes a patient as follows: "He was a lean, pale boy with a feeble circulation and soft pulse."

Guilblain emphasizes the importance of distinguishing essential orthostatic albuminuria from the intermittent albuminuria of chronic nephritis, from digestive or dyspeptic albuminuria, from pretuberculous albuminuria described by Teissier,⁴⁹ from cyclic albuminuria (Pavy), from fatigue or physiological albuminuria, from the albuminuria accompanying hemoglobinuria, and from metabolic albuminuria.

It is not uncommon to observe an intermittence in the albuminuria present with chronic nephritis. It can, however, in the majority of cases be readily distinguished from the true orthostatic albuminuria. Digestive or dyspeptic albuminuria can be readily distinguished by its association with meals or with digestive upsets. The pretuberculous albuminuria of Teissier invariably exhibits albuminuria in the early morning hours. The cyclic albuminuria of Pavy may or may not fall into the class under discussion. Fatigue or physiological albuminuria has been carefully studied by Lommel⁵⁰ and by von Leube.⁵¹ Lommel found among 587 apprentices, aged 14 to 18 years, that albuminuria was present in 18.9 of the cases. Von Leube states that this

45. Dukes: Brit. Med. Jour., 1878, ii, 794.

46. This assumption is not in accord with the observation that there is a continuous elevation of arterial (systolic) blood-pressure from the sixth to the eighteenth year. See Potain, *La pression artérielle de l'homme*, Paris, 1902, p. 102.

47. Craig: Brit. Med. Jour., 1886, i, 333.

48. Herringham: Brit. Med. Jour., 1891, i, 218.

49. Teissier: *Congres de Méd.*, Lyon, 1894, L. Savy, Lyon, 1895.

50. Lommel: *Deutsch. Arch. f. klin. Med.*, 1903, lxxviii, 541.

51. Von Leube: *Deutsch. med. Wehnschr. (Vereins-Beilage)*, 1902, xxviii, 309.

form of albuminuria is present in from 20 to 50 per cent. of cases observed. It may, of course, be brought on as the result of fatigue, and may or may not include the cases of orthostatic albuminuria. Metabolic albuminuria has been emphasized by Charrin.⁵² Charrin observed that the blood-pressure, freezing-point of the urine, toxicity of the urine, temperature of the urine, the absorption of oxygen, and the rectal temperature, follow in general the output of albumin. He maintains that all these phenomena are the result of metabolism, and hence that albuminuria may be regarded as a nutritional disease. The albuminuria coincident to hemoglobinuria has been already considered in connection with the work of Ralfe.

Throughout the period at present under discussion, observers were divided between the views that all albuminuria is pathological, and that some cases are harmless. The majority, however, are inclined to the latter view. Casts in the urine might be regarded as of important pathological moment. Most observers, however, have been unable to observe their presence, although some have found hyaline casts. Huger⁵³ observed two cases. In both he was able to find hyaline casts, and believes that a careful examination of the urine will, in all cases, reveal their presence.

The prognosis for orthostatic albuminuria is, according to Guilblain, excellent. We thus see a distinct change in the point of view over that held at the time Dubreuilh prepared his paper. The presence of albuminuria in such a large percentage of cases has made the subject of great interest from the point of view of life-insurance. Therefore, the discussion of this aspect of the subject has become very general, and we find that writers are inclined to a broader interpretation of albuminuria than formerly. Shepherd,⁵⁴ in 1888, reported the results from 35,000 examinations of urine. He noted that the brain-workers showed a larger percentage of albuminuria than the muscle-workers, that in the large majority of cases albuminuria is not associated with renal disease, and that in the matter of life-insurance, albuminuria should be looked on as a symptom only, and acceptance or rejection of the risk should depend on the gravity of the case. Tyson, in a paper read before the Association of American Physicians in 1888,⁵⁵ came to a similar conclusion. This paper was discussed editorially in the *British Medical Journal* the following year.⁵⁶ The writer admitted the difficulty of examination in

52. Charrin: Jour. de Physiol. et path. gén., 1901, iii, 58.

53. Huger: Bull. Johns Hopkins Hosp., 1902, xiii, 75.

54. Shepherd: Boston Med. and Surg. Jour., 1888, cxviii, 575.

55. Tyson: Tr. Assn. Am. Physicians, 1888, 171.

56. Editorial: Brit. Med. Jour., 1889, i, 26.

such cases, but concluded that albuminuria, as such, was not a sufficient reason to refuse insurance.

The fact that variation in arterial tension was not sufficient to explain the presence of albumin in the urine, together with the difficulty of accounting for the phenomenon on the ground of a venous stasis, since albumin is not present in such cases in the sitting posture, led to the suggestion that a movable kidney might be the proper explanation. This idea was first suggested by Sutherland⁵⁷ in America in 1903, and was advanced by Guiblain at about the same time. This belief has not, however, received wide acceptance, although one case has been recently reported by Blum,⁵⁸ in which it was found that an aberrant renal artery was pressed on by the ureter, thus producing albuminuria.

Throughout this period (1887 to 1903), numerous observers suggested the idea that vasomotor instability might be the etiological factor in question, but Edel was the first to bring forward definite evidence substantiating this conception. In his first paper, published in 1901, he noted that diuretics caused the albumin to disappear from the urine. Hot baths also decreased the amount of albumin, under which condition he observed that the skin was flushed, the pulse fuller and faster, and that the amount of albumin was inversely related to the amount of urine. Pribram⁵⁹ had also observed fifteen cases of orthostatic albuminuria in which the specific gravity always varied directly as the albumin present. Edel noted also that moderate exercise without fatigue improved the strength of the pulse by stimulating the heart action and decreased the amount of albumin, causing also an increase in the amount of urine secreted. He therefore suggested as a rational therapeutic measure that the heart should be strengthened by careful exercise, that in no case should the subject be kept in bed, and that rich diuretic food should be indulged in. In his second paper published in 1903, he reported observations on the blood-pressure. In such cases, the effect of warm baths on normal individuals was to cause a slight fall in blood-pressure—10 mm. during the bath, which rose 25 mm. after the bath. Albuminurics, however, failed to show this rise in pressure after the bath, and had sensations of relaxation and fatigue instead of feeling refreshed, as was the case in normal individuals. As the result of cold sponges, the blood-pressure of albuminurics was not as responsive as in the case of controls, but tended to remain constant, or sometimes to fall, while in the normal cases there was usually a rise. Exercise (climbing

57. Sutherland: *Am. Jour. Med. Sc.*, 1903, cxxvi, 289.

58. Blum: *Wien. med. Wchnschr.*, 1908, xxi, 503.

59. Pribram: *Centralbl. f. inn. Med.*, 1889, xx, 482.

stairs) produced a much less pronounced effect on the blood-pressure of albuminurics than on that of normal individuals, as shown by his figures here given (Table 3).

TABLE 3.—EFFECT OF EXERCISE ON BLOOD-PRESSURE OF NORMAL AND ALBUMINURIC INDIVIDUALS

	Before.	Just After.	2 Min. After.	20 Min After.
Normal	136	205	181	136
Abnormal—Morning		+ 37	(not stated)	(still more)
Afternoon ..		+ 17	+ 16	0

Just after bicycle-riding the blood-pressure was high. Fifteen minutes after riding, however, the blood-pressure was low again and albumin made its appearance. When normal individuals changed from the sitting to the standing posture, the blood-pressure rose and seemed to remain elevated, while in the case of albuminurics the blood-pressure did not rise and sometimes fell. From these observations Edel infers that orthostatic albuminuria depends on the inability of the cardiovascular system to respond to ordinary changes. He believes that the heart and vascular system are very important in fatigue, and the fact that subjects suffering with albuminuria are readily fatigued tends strongly to support the belief that the two are intimately associated.

THIRD PERIOD

The third period in the development of our knowledge of orthostatic albuminuria, extending from 1903 up to the present time (1909), offers only three new suggestions for the etiology: that presented by Teissier,⁶⁰ implying a developmental defect in the glomerulus;⁶¹ that offered by Erlanger and Hooker,⁶² and that of Jehle.⁶³ Teissier, in a paper published in 1905, is careful to distinguish between true orthostatic albuminuria and mixed albuminuria. The former, he says, is characterized by the juvenile appearance of the patient, a poorly developed vascular system and small heart, low arterial pressure and a subnormal body weight. Such cases may or may not give a history of infection. When the patient changes from the lying to the standing position, albumin promptly makes its appearance in the urine and disappears as quickly when he lies down.

60. Teissier: *Revue de Med.*, 1905, xxv, 233.

61. This is practically the suggestion of von Leube, but stated with more boldness and decision.

62. Erlanger and Hooker: *Johns Hopkins Hosp. Rep.*, 1904, xii, 145.

63. Jehle: *München. Med. Wchnschr.*, 1908, lv, 12.

Nervous symptoms are frequently associated. In such cases the amount of albumin excreted varies from 0.5 to 4 gm. per liter. The protein is serum albumin. Globulin is only exceptionally present. If any protein is associated with the serum albumin it is practically always nucleo-albumin.⁶⁴ In agreement with von Leube, he conceives of permeable, semipermeable and impermeable kidneys, and believes that orthostatic albuminuria falls into the class of semipermeable kidneys, due to a defect in the development of the glomerulus. Jehle observed a case of orthostatic albuminuria, which, however, exhibited casts and blood elements. From the study of this case, he came to the conclusion that the albuminuria was caused by lordosis which resulted in a pressure on either the renal vessels or the ureter. With this conception of the cause of the albuminuria, he favored exercise as a therapeutic agent, because it would strengthen the muscles of the back and thus improve the condition of lordosis and coincidentally the albuminuria. Nothmann⁶⁵ has recently confirmed Jehle's observation, that lordosis may be the cause of orthostatic albuminuria. He has succeeded in producing albuminuria by artificially induced lordosis. Observations on the cadaver and on rabbits indicate that curvature of the spine could disturb the normal position of the kidneys to an extent sufficient to explain the disturbances in the circulation, which are evidently responsible for the albuminuria. I shall later on refer to the work of Erlanger and Hooker.

It is interesting to note the effect of athletic exercise on the appearance of albumin. Dunhill and Patterson,⁶⁶ in Australia in 1902, and W. Collier,⁶⁷ in England in 1907, investigated the urines of boat crews and found that albumin was invariably present after the races.

Rose Bradford, in an address before the British Medical Association in 1907,⁶⁸ reached the conclusion that there was no adequate explanation of the phenomenon under discussion, except that of vasomotor insufficiency.

Adam Loeb,⁶⁹ in Germany in 1905, studied the behavior of the quotient Δ/NaCl in cases of nephritis, cardiac disease and orthostatic albuminuria. On the theoretical assumption that an increase in the quotient means a decreased flow of blood through the kidneys and a decrease in the quotient means an increased flow of blood through the kidneys, he found that those with orthostatic albuminuria and those

64. This statement has been entirely substantiated by other observers.

65. Nothmann: *Arch. f. Kinderheilk.*, 1909, xlix, 216.

66. Dunhill and Patterson: *Intercol. Med. Jour. Australasia*, 1902, vii, 334.

67. Collier: *Brit. Med. Jour.*, 1907, i, 4.

68. Bradford: *Brit. Med. Jour.*, 1907, i, 725.

69. Loeb: *Deutsch. Arch. f. klin. Med.*, 1905, lxxxiii, 452.

with cardiac disease both showed an increase of Δ/NaCl , together with a lessened excretion of sodium chlorid and water on the patient's assuming the upright position which was accompanied by the appearance of albumin in the urine. These conditions did not hold for nephritis. Philippson,⁷⁰ however, has recently been unable to make this sharp distinction. Loeb thus believed that the condition of albuminuria was dependent on the cardiovascular disturbances, probably vasomotor in origin, which found their origin in infectious diseases.

Porges and Pribram⁷¹ and Pelnar⁷² studied the effect on the albuminuria of substances which would tend to alter the circulation, such as coffee, strychnin, diuretin, chloral hydrate, morphin, adrenalin, purgatives, severe exercise, etc. No positive results were obtained. Porges and Pribram determined the blood-pressure with Gärtner's tonometer. Since they were unable to note any great changes in the arterial pressure, and since venous stasis and movable kidney were excluded, they concluded that the condition must be a result of constrictor spasm of the renal artery.

In 1904 Erlanger and Hooker published an extensive study of blood-pressure in a case of orthostatic albuminuria, using the Erlanger sphygmomanometer.⁷³ Blood-pressure changes were induced by various physiological procedures, such as muscular exertion, compression of the legs with Crile's pneumatic suit, cold and hot baths, etc. As a result of this investigation, the only factor which was found to vary directly as the appearance of the albumin and inversely as the amount of urine excreted was the pulse-pressure. The pulse-pressure was found to vary in a normal individual in the same direction as in the albuminuric, but not, however, to the same extent. It seems probable, therefore, that the permeability of the kidney of a person suffering with orthostatic albuminuria must be greater than in a normal individual, and that the appearance or non-appearance of albumin is dependent on the nutrition (oxygen supply?) of the organ, brought about by variations in the amplitude of the pulse.⁷⁴

In a paper published by Leonard Williams in 1908,⁷⁵ the suggestion is made that orthostatic albuminuria, since it is common in the early

70. Philippson: *Jahrb. f. Kinderh.*, 1906, lxiii, 174.

71. Porges and Pribram: *Deutsch. Arch. f. klin. Med.*, 1907, xc, 367.

72. Pelnar: *Centralbl. f. inn. Med.*, 1905, xxvi, 1025.

73. For a description of the instrument see Erlanger, *Johns Hopkins Hosp. Rep.*, 1904, xii, 53.

74. This may be regarded as a very conservative conclusion, since it fails to take into consideration exercise albuminuria, as well as the peculiar sensitiveness of the normal kidney to interference with its circulation.

75. Williams: *Clin. Jour.*, 1908, xxxii, 23.

years of life, is due to an incomplete functional development of the vasomotor system. He cites the fact that the urine of new-born children almost always contains albumin, which disappears from the urine after the vasomotor system has become adapted to its new requirements.

In 1907 Heubner presented before the Medical Society in Berlin the results of an autopsy on a young girl who had been suffering with orthostatic albuminuria.⁷⁶ Only a single minute lesion, 1 by 1.5 mm. in extent, was found in the pole of the right kidney. This is the only case of autopsy found in the literature. Heubner does not believe that the lesion in itself was sufficient to account for the albuminuria present. The child came of a tuberculous family, had had measles and scarlatina and had been operated on for adenoids one year before she came under observation. Her first appearance was in 1903, when she came to the clinic for a cough and a swelling of the neck. The urine at this time was free from albumin. In the following year, May, 1904, the patient returned complaining of headache, as well as the former symptoms. At this time she showed slight edema of the eyelids and feet and exhibited orthostatic albuminuria. In November of the same year her eyesight had become weak, and choked disc was present with attacks of vomiting. A diagnosis of cerebellar tumor with secondary hydrocephalus was made at this time. The albuminuria was more severe, but still orthostatic in type. Early in 1905 the patient was operated on. She died in October of the same year. Throughout the time during which she was under observation no casts were found in the urine.

This report was followed by a lengthy discussion by Senator, Langstein, Baginsky, Furbringer, Hansemann, Orth and others.⁷⁷ The consensus of opinion was that the lesion was insufficient to account for the albuminuria observed.

Finally, I should mention the work of Wright and Ross,⁷⁸ who have found it possible to cure patients with orthostatic albuminuria by the administration of calcium. They made use of this treatment on the assumption that the albuminuria is the result of an abnormality in the blood. Calcium acts to hasten the coagulation of blood and presumably increases the viscosity. Furthermore, the administration of calcium lactate served, in the hands of these observers, to differentiate renal from non-renal albuminuria, the excretion of albumin in the former not being affected.⁷⁹ Teissier's observation of the coincidence of skin troubles in

76. Heubner: Berl. klin. Wehnschr., 1907, xlv, 1.

77. Berl. klin. Wehnschr., 1907, xlv, 61.

78. Wright and Ross: Lancet, London, 1905, ii, 1164.

79. I have been unable to confirm this in a case recently under observation.

such cases, and the theory advanced by Ralfe, are of interest in connection with the work of Wright and of Luff.⁸⁰ The latter has found, following the suggestions of Wright, that calcium lactate is a very efficient therapeutic agent in persistent cases of chilblains, boils associated with cold hands and feet, urticaria, erythema, lichen planus, pruritus, hemoglobinuria, etc., complaints which, he discovered, were, in all his cases, associated with retarded blood-coagulation. No determinations of blood-pressure have been reported for cases such as those described by Wright, and it is not known what effect the calcium has on the physics of the circulation.⁸¹

Throughout this discussion it must have been evident that the variations in the point of view presented by different observers might be accounted for by variation in the cases observed. There can be no doubt, however, that it is possible for albumin to make its appearance in the urine without the consequent assumption of pathological conditions in the kidneys. We should not be justified, however, in ignoring the opinion of Senator, who has probably given more attention to diseases of the kidney than any man now living, and who has, throughout the years in which albuminuria has been so hotly discussed, maintained unflinchingly his belief that protein in the urine must be regarded as evidence of pathological conditions in the kidney. I quote from a recent address:

With the lapse of time I am only more strongly confirmed in the view, which I expressed years ago, that a slight irritation or inflammatory condition, which may progress toward recovery or toward a diffuse chronic nephritis, is responsible for most, if not all, of the cases of "cyclic" or orthostatic albuminuria.⁸²

Of the numerous theories dealing with the causation of orthostatic albuminuria, that of a vasomotor instability stands out prominently to account for the typical cases. The work of Edel, of Loeb, and of Erlanger and Hooker gives direct support to this view. Loeb, Linossier and Lemoine, and Erlanger and Hooker were able to show that the kidneys in orthostatic albuminuria did not excrete the ordinary urinary constituents normally. Edel reached the conclusion that a low systolic

80. Luff: Brit. Med. Jour., 1909, i, 261.

81. It is of interest in this connection to note that the case observed by Erlanger and Hooker was subject to eczema. The attacks of eczema ceased, however, approximately coincidently with the natural disappearance of the albuminuria.

82. Ich bin somit je länger je mehr in der schon vor Jahren von mir ausgesprochenen ansicht bestärkt worden, dass, wenn nicht allen, so doch den allermeisten Fällen von "cyklischer," namentlich orthostatischer (orthotischer) Albuminurie ein leichter Reiz—oder entzündlicher Zustand in den Nieren zugrunde liegt, welcher in Heilung übergehen, aber auch bis zu einer diffusen chronischen Nephritis sich weiter entwickeln kann. Senator: Deutsch. med. Wehnschr., 1904, xxx, 1833.

blood-pressure was an invariable concomitant of albuminuria. Erlanger and Hooker were unable to observe any consistent relationship between the appearance of albumin and the systolic or diastolic blood-pressure or the velocity of blood flow in the aorta. There was, however, an invariable inverse relationship between the appearance of albumin and the magnitude of the pulse-pressure. Since, however, the behavior of the pulse-pressure, under varying conditions, was qualitatively the same in the control and in the albuminuric, no sharp line of demarcation could be drawn. The suggestion was tentatively advanced that variations in the magnitude of the pulse-pressure might influence the oxygen supply to the renal epithelium, and so alter its functioning properties. In the case under observation, the pulse-pressure was uniformly less than that of the normal individual, and showed, as did the systolic and diastolic blood-pressure, a marked tendency to be less stable. This tendency was repeatedly emphasized by attacks of syncope during the periods of observation. When we consider the phenomenal sensitiveness of the normal kidneys of animals to the slightest alteration in their blood-supply (momentary clamping of the renal artery or vein, etc.), some support is added to the suggestion of a transient nutritional disturbance. Definite proof must rest, however, on the successful perfusion of the isolated kidney.

Recently I have collaborated in the observation of a second similar case, the results of which have not yet been published. It is of interest to state here that this recent work corroborates entirely that done with Dr. Erlanger. It may be of interest to state also that the patient studied by Erlanger and Hooker has entirely recovered from his albuminuria.

That the albumin of orthostatic albuminuria and the post-exercise albuminuria first observed by Dunhill and Patterson may result from the same immediate cause, namely, a decrease of pulse-pressure, is indicated by recent investigations of exercise on the arterial blood-pressure. Barach, Boyce and Savage determined the systolic and diastolic pressures in a number of individuals before and after Marathon races.⁸³ In these individuals the urine was normal before the runs. After the exertion the urine contained casts, blood, albumin and acetone bodies. This change in the urine was accompanied by a marked diminution in the amplitude of the pulse-pressure. In this laboratory shorter runs have been observed to result in albuminuria. In these cases both systolic and diastolic pressures were greatly increased immediately after the exercise, the systolic the more so that the pulse-pressure was increased. This increase gave way at once to a fall of both pressures accompanied by a

83. Reported before the American Physiological Society, December, 1909.

decrease of pulse-pressure. Faint traces of albumin were found in the first urines voided after the exercise. The albumin increased in amount with the post-exercise fall of pulse-pressure (independent of the changes in systolic and diastolic pressures) and disappeared with the return of this factor to normal. It would appear, therefore, that orthostatic albuminuria is not necessarily directly associated with a permanent impairment of renal function.

Johns Hopkins University.

SUPPLEMENTARY BIBLIOGRAPHY

Additional references to the literature not directly used in the text are the following:

- Barré: Thesis, Paris, 1903.
 Beck: Am. Jour. Med. Sc., 1903, cxxvi, 466.
 Black: Brit. Med. Jour., 1889, i, 329.
 Capitan: Compt. rend. Soc. biol., 1892, xlv, 144.
 Collins: Lancet, London, 1886, i, 346.
 Cuffer and Gaston: Rev. de méd., 1891, xi, 89.
 Dresser: Deutsch. Med. Wehnschr. (Vereins-Beilage), 1902, xxviii, 322.
 Dukes: Brit. Med. Jour., 1878, ii, 794.
 Editorial: Lancet, London, 1887, i, 639.
 Finot: Compt. rend. Soc. biol., 1892, xlv, 134.
 Flensburg: Skand. Arch. f. Physiol., 1893, iv, 411.
 Fournier: Thesis, Paris, 1897-98.
 Freud: Thesis, Göttingen, 1886.
 Fürbringer: Deutsch. Med. Wehnschr., 1905, xxxi, 777.
 Goodhart: Brit. Med. Jour., 1890, i, 1121.
 Hawkins: Brit. Med. Jour., 1899, ii, 1598.
 Heuser: Berl. klin. Wehnschr., 1903, xl, 1152.
 Jacobson: Berl. klin. Wehnschr., 1903, xl, 914.
 Keller: Jahrb. f. kinderh., 1897, xlv, 64.
 Klemperer: Berl. klin. Wehnschr., 1889, xxvi, 864.
 Knecht: Deutsch. Arch. f. klin. Med., 1905, lxxxiii, 266.
 Krieg: Thesis, Freiburg, 1900.
 Lecorché and Talamon: Centralbl. f. inn. Med., 1893, xiv, 127.
 Lokie: Brit. Med. Jour., 1886, i, 1059.
 Mörner: Skand. Arch. f. Physiol., 1895, vi, 332.
 Neukirch: Deutsch. Arch. f. klin. Med., 1905, lxxxviii, 165.
 Von Noorden: Deutsch. Arch. f. klin. Med., 1886, xxxviii, 205.
 Ostwalt: Compt. rend. Soc. biol., 1897, xlix, 663.
 Pavy: Lancet, London, 1885, ii, 706.
 Posner: Ztschr. f. klin. Med., 1904, liii, 42.
 Pribram: Prag. Med. Wehnschr., 1904, xxix, Nos. 1-3.
 Quincke: Arch. f. exper. Path. u. Pharmakol., 1893, xxxii, 211.
 Ralfe: Lancet, London, 1888, ii, 953.
 Reck: Thesis, Jena, 1888.
 Rudolf: Centralbl. f. inn. Med., 1900, xxi, 225.
 Schön: Jahrb. f. kinderh., 1896, xli, 307.
 Senator: Die Albuminurie im gesunden und kranken Zustande, Aug. Hirschwald, Berlin, 1882.
 Stejskal: Wien. klin. Wehnschr., 1908, xxi, 493.
 Ullmann: Berl. klin. Wehnschr., 1907, xlv, 130.
 Unverricht: München. Med. Wehnschr., 1896, xlvii, 1172.