

# THE CLINICAL SIGNIFICANCE OF AN INCREASED NONPROTEIN NITROGEN CONTENT OF THE BLOOD

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The nonprotein nitrogen of the blood exists in a number of heterogeneous compounds which are chiefly urea, amino acid, uric acid, creatinine, and creatine, and in a group of nitrogenous substances, the composition of which is little known and which are collectively spoken of as the undetermined nitrogen of the blood. Urea is quantitatively the most important component and, because of its ready solubility and diffusibility, it is distributed quite evenly between the cells and the plasma. The amino acids compose the next largest fraction and appear in greater concentration in the cells. Uric acid comprises only a small fraction of the total nonprotein nitrogen and is apparently evenly divided between the corpuscles and the plasma. Creatinine appears in small amounts in the plasma and in larger amounts in the corpuscles, and creatine is entirely confined to the cells. The undetermined nitrogen factor which comprises approximately one-third of the total nonprotein nitrogen in the blood is largely confined to the cells.

The total nonprotein nitrogen of normal whole blood ranges between 28 and 42 mg. per 100 cc. with an average of 32 mg. The urea nitrogen varies between 9 and 16 mg. per 100 cc. with an average of 12 mg. with urea values between 20 and 35 mg. The amino acid nitrogen varies between 6 and 8 mg. per 100 cc. with an average of 6 mg., and the undetermined nitrogen comprises between 10 and 18 mg. with an average of 14 mg. Uric acid determinations on normal blood range from 1.5 to 4 mg. per 100 cc. The normal concentration of creatinine in the blood is generally regarded as being from 1 to 2 mg. per 100 cc.

Concentration of the nonprotein nitrogen in the lymph in animals has been shown to be approximately the same as that of the blood serum both before and after bilateral nephrectomy. It has also been shown that the nonprotein nitrogen of transudates is approximately the same as that of the blood serum and this is also true with regard to synovial fluid. Spinal fluid, on the other hand, may contain considerably smaller amounts, partially due to the almost complete absence of uric acid. It has been shown that the various tissues of the body, particularly muscular tissue, contain greater concentrations of total nonprotein nitrogen than does the blood. It is believed that this excess nitrogen in the tissues is not held in simple diffusion but represents products of catabolism or anabolism of materials of more importance to the cellular economy. With an increase in the nonprotein nitrogen level

of the blood in nephritic conditions, it has been found that the pathological accumulation of nitrogen generally becomes distributed equally between the blood and the tissue but that the total nonprotein nitrogen content of the tissue still is higher than the nonprotein nitrogen in the blood. This excess of nonprotein nitrogen in the tissues over the nonprotein nitrogen in the blood is due to nitrogenous extractives, especially creatinine.

Theoretically, the nonprotein nitrogen level of the blood in the body at any time is dependent upon the amounts produced in the body in relation to the amount excreted through the various excretory channels. An increased production of any of the constituents could, therefore, cause an increase in the total amount. Actually, any considerable changes in the nonprotein nitrogen level are due to alterations of the concentration of urea or undetermined nitrogen, or both. Urea represents the chief end product of protein catabolism and under physiological and nearly all pathological conditions the values for urea and nonprotein nitrogen run parallel. The amino acid nitrogen in the blood is little affected by most physiological and pathological conditions and displays an amazing stability under various metabolic abnormalities, suggesting that there are regulatory mechanisms which provide a great margin of safety for this essential material. The greatest factor is apparently in the hepatic mechanism and only under conditions of severe damage to the liver do marked increases of amino acids occur in the blood.

The amount of uric acid in the blood is so small that even considerable fluctuations have little effect on the total nonprotein nitrogen and the same is true of creatine and creatinine. Creatinine increases in the terminal stages of renal failure only when the blood urea is already elevated. The undetermined nitrogen factor also increases considerably in nephritis and other diseases that cause elevation of the total nonprotein nitrogen but usually less than the urea nitrogen. Consequently, the level of blood urea may be taken as an index of the nonprotein nitrogen level of the blood.

The other chief factor determining the nonprotein nitrogen level of the blood at any time is its rate of removal from the body. The chief channel for the excretion of nitrogen is the kidney. The normal kidney is able to concentrate the urea of approximately 80 cc. of blood into 1 cc. of urine. With reduction in renal efficiency, this power decreases and larger amounts of urine must be excreted in order to remove nitrogen from the body without an increase of its level in the blood. Diuresis thus may overcome renal inefficiency for a time but, even in nephritis, the limit beyond which diuresis no longer increases the excretion of urea seems to be about three liters a day. There is, of course, a certain amount of nitrogen excreted in the feces and in perspiration,

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The nitrogen in the feces, however, is not catabolic nitrogen and it has been shown that it does not increase to any degree even in conditions that increase the nonprotein nitrogen content of the blood. It is increased in high protein feedings only when proteins that are not assimilable are taken, and in diarrhea where it is believed that the increased nitrogen in the feces represents secretions from the intestinal mucosa rather than an actual excretion from the body. The use of cathartics, therefore, in attempting to treat elevations of nonprotein nitrogen in the blood is illogical, particularly when it is remembered that the incident diarrhea with loss of fluids to the body may increase the factor of dehydration from which these patients so frequently suffer, thus tending to lessen the renal flow.

Perspiration contains a certain amount of urea and nonprotein nitrogen and, with profuse diaphoresis, the cutaneous excretion of nitrogen may be considerable but it is doubtful clinically whether this function is of much value in renal inefficiency. For all practical purposes, therefore, it may be assumed that excretion of nitrogenous metabolites depends entirely upon renal efficiency. Besides the actual renal epithelial activity, this implies an adequate urinary volume since oliguria may in itself produce failure of excretion of nitrogen in a normal kidney. It must be remembered that in nearly all clinical cases, disturbances of nonprotein nitrogen are due not to single factors but to combinations in varying degrees.

There are certain variations of nonprotein nitrogen levels which are of physiological origin. Thus, after a meal rich in protein, the nonprotein nitrogen level of the blood rises gradually, reaching a maximum within three to four hours, and subsequently falling to the original level. The excretion of nitrogen in the urine follows closely the changes in the blood. In renal inefficiency it has been shown that the maximum is not attained for a longer period and takes longer to return to the fasting level, thus simulating the changes in the glucose tolerance curve in diabetes. The postprandial rise is caused by the delivery to the blood of extra amounts of amino acid from protein digestion and of urea from protein catabolism. If large amounts of fluids have been taken with the food, it is possible that the diuresis which occurs may prevent any postprandial rise. Because of the influence of dietary proteins, determination of the blood urea is usually considered most correct when taken in the morning during the fasting state. However, it must be remembered that in many cases the blood urea will be found highest at this time presumably due to nocturnal oliguria. Physical exercise, especially with food and water deprivation, markedly increases nitro-

genous wastes in the blood and may increase nonprotein nitrogen levels but, if the urinary volume and renal efficiency are adequate, the rise is slight and transitory.

Certain endocrine dysfunctions tend to disturb the nonprotein nitrogen level although usually not to marked degrees. Hyperthyroidism increases the demands of the body for fuel and if this is not supplied with a high caloric intake, protein in the body is used in undue amounts, thus tending to increase the level of nitrogen in the blood. Increased renal activity in the presence of sufficient urinary volume will prevent any clinical increase under such circumstances unless there should be renal damage. After parathyroidectomy it has been shown that the nonprotein nitrogen in the blood and the nitrogen in the urine increase particularly during convulsions and, according to a paper published by Haden<sup>1</sup> some years ago, the rise of the nonprotein nitrogen level of the blood under such circumstances is almost entirely confined to the undetermined nitrogen fraction. With convulsions, of course, there is markedly increased production of nitrogenous metabolites from muscular activity. This is frequently seen in convulsions in uremia. The nonprotein nitrogen level of the blood is found to be elevated somewhat in the terminal stages of Addison's disease. In diabetes mellitus when carbohydrate metabolism is poorly carried on and secondary fat metabolism is affected, there is liable to be wasteful burning of protein tissue in order to supply energy, thus tending to increase the nitrogenous waste in the blood. With an accompanying renal lesion or dehydration, the nonprotein nitrogen level of the blood may rise considerably. This is especially evident in precoma but is usually prevented by the marked diuresis which is characteristic of the disease.

Disturbances of the liver affect the partition rather than the total concentration of nonprotein nitrogen in the blood and in urine. After total hepatectomy, amino acid nitrogen rises while the urea nitrogen falls because in the absence of the liver the organism loses the power to diaminate amino acids and to form urea. This is also true in the terminal phases of acute yellow atrophy, but it is recognized that the hepatic reserve prevents such a condition existing until just before death. In advanced cirrhosis of the liver, in some hepatic conditions requiring surgery, and in diseases of the gallbladder and ducts, the nonprotein nitrogen level of the blood is frequently elevated. It is unlikely that these accumulations of nitrogen are referable to hepatic injury. They are more likely to be related to disturbances of renal function, deficient urinary volume, or excessive breakdown of protein from associated conditions which will be discussed later.

Following severe hemorrhage, transitory increases of nonprotein nitrogen in the blood with blood urea readings up to 200 mg. per 100 cc.

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have been noted which have been shown to be unrelated to the anemia itself, inasmuch as they are corrected long before the blood elements have been restored. This may well be related to shock where fluid is lost from the blood and concentration of the blood occurs. Dehydration following hemorrhage certainly appears to be a factor in this increase. There is also the question of increased protein metabolism from the absorption of blood from the bowel. It has also been repeatedly shown that where plasma proteins are markedly decreased, the endogenous protein catabolism is increased. Then, too, it has been shown that the nonprotein nitrogen content of the tissue fluids is somewhat higher than that of the blood. Thus, when the blood volume is formed from the tissue fluids, the tendency may be to increase somewhat the nonprotein nitrogen level. This is in accord with the well-known fact that after venesection for uremia the nonprotein nitrogen level is usually higher than before venesection.

Borst<sup>2</sup>, in a discussion of the basis for the increase in nonprotein nitrogen level following gastro-intestinal hemorrhage, states that the azotemia is usually associated with a hyperchloremia and a reduced excretion of urinary chloride. He cites the increased catabolism of body proteins in such patients when they are insufficiently fed, as well as the increased formation of urea from the blood in the intestines, and points out that the azotemia in itself results in a relative polyuria with maximal concentration of urea in the urine which may tend to restore the normal level. If, however, there is dehydration or shock from operation, the output of urine is decreased and the blood urea tends to rise. The post-hemorrhagic dilution of blood and consequent reduction of nonprotein nitrogen is retarded not only by the diuresis mentioned above and the restriction of intake of fluids which these patients usually undergo, but also by the low albumin content of the plasma following severe hemorrhage which lessens the power of the blood to draw fluid from the tissue spaces, and by the capillary damage associated with shock which readily allows fluid to leak from the vessels. It has been shown that sodium and chloride are retained when post-hemorrhagic dilution is in progress, while an increased excretion of potassium in the urine is observed. This is regarded as part of a mechanism established for the purpose of restoring the normal filling of the arterial system by way of an augmentation of the total extracellular fluid and therefore the blood plasma.

In the febrile stage of most acute infectious diseases, both the total metabolism and the nitrogen metabolism are considerably increased.

The loss of nitrogen in the urine cannot be entirely overcome by increased caloric feeding and it is concluded therefore that the greater protein catabolism in febrile infection is due not only to increased energy requirements but also to an active destruction of tissue. This toxic destruction of protein can be lessened but not abolished by the administration of sufficient fat and carbohydrates to provide for the energy requirements. The toxemia is somewhat parallel to the pyrexia and, of course, with high fever it is impossible to make patients who are ill consume sufficient calories. There is, therefore, a definite tendency for nitrogen catabolism to increase in the presence of fever due to this so-called destruction of proteins which is regarded as being due to an actual autolysis of tissue. The extra nitrogen appears in the urine in the form of urea plus ammonia, with some observers claiming also that excretion of amino acid rises under similar circumstances. If there is an accompanying renal lesion or an oliguria, it is evident that there will soon be an increase in the nonprotein nitrogen in the blood. This condition is very frequently seen in lobar pneumonia and may be regarded as being of some prognostic significance. There is always the question of an accompanying renal lesion, but it is likely that with normal kidney function a moderate elevation in protein catabolism and nonprotein nitrogen in the blood is frequently observed in severe pneumonia. It usually does not reach levels more than double the ordinary normal level unless there is definite renal damage. The value of the ingestion of large amounts of fluid in such cases becomes apparent inasmuch as it provides a vehicle for the excretion of the waste products and tends to restore normal values in the blood. Studies of urinary nitrogen under such circumstances frequently show large amounts of from 16 to 22 gm. per liter which in itself is evidence of efficient renal function, and also evidence of markedly increased nitrogen catabolism within the body. Haden<sup>3</sup> believes that the retention of nonprotein nitrogen in pneumonia is a toxic manifestation associated with the low serum chlorides so characteristic of the disease and he feels that the administration of sodium chloride has a specific beneficial effect—alleviating symptoms and diminishing retention of nitrogen. Van Slyke<sup>4</sup>, however, believes that the effect of salt solutions is chiefly that of combatting dehydration and promoting diuresis.

It has been repeatedly shown that obstructions in the alimentary canal at any point from the esophagus to the rectum will cause an increased concentration of nonprotein nitrogen in the blood at times up to 300 mg. per 100 cc. According to some observers, the chief increase is in the undetermined nitrogen fraction rather than in urea. The earlier explanations of this phenomenon infer that the rises following intestinal obstruction were due to the absorption of toxic products of protein digestion from the obstructed loops of intestine, but it has been shown



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that azotemia develops when the obstruction is at or above the pylorus, preventing the passage of protein to the intestine but not through it. Again the question of the efficiency of the kidneys has been raised, but it has been shown that under such circumstances, markedly increased amounts of nitrogen appeared in the urine and it has been shown frequently that the kidney can concentrate the urine to a high degree, even in spite of the oliguria and, in fact, may excrete abnormal amounts of nitrogen. It is, therefore, clear that the chief cause for the accumulation of nonprotein nitrogen in intestinal obstruction is due to an increased destruction of proteins and to some extent to dehydration. It has been well shown that such accumulation of nitrogen can be mitigated by the parenteral or rectal administration of sodium chloride solution.

In other surgical conditions of the abdomen, particularly associated with peritonitis, an azotemia is frequently seen. In this case a functional obstruction has occurred and the situation is aggravated by the dehydration from vomiting. The underlying infection probably plays a contributory role by adding to the protein destruction. Persistent vomiting in itself, even in the absence of obstruction of the alimentary tract, if sufficiently prolonged and severe to produce dehydration and starvation, will appreciably raise the nonprotein nitrogen level of the blood. Severe diarrhea, also, because of extreme water loss and dehydration, may be followed by an increase of the nonprotein nitrogen level of the blood, the effect being exaggerated by toxic destruction of nitrogen when associated with infection.

Uncomplicated heart failure may result in slightly increased nonprotein nitrogen levels of the blood, apparently due to a decrease in renal circulation and a relative oliguria. Digitalization in such cases may rapidly result in normal readings. Heart failure, however, complicating acute infection, may cause rapid accumulations of nitrogen in the blood and in nephritis the development of cardiac decompensation may cause it to rise rapidly. There seems to be a greater tendency to azotemia in syphilitic heart disease with decompensation perhaps because circulatory failure in this condition is a relatively late event. In hypertensive and arteriosclerotic heart disease with failure, increased nonprotein nitrogen levels are frequent, probably because of an associated sclerotic renal change. In bacterial endocarditis, a high nonprotein nitrogen content is a frequent occurrence and here the increased toxic destruction of protein associated with infection, as well as the renal lesions which may accompany the disease, probably afford an explanation.

The greatest elevations of nonprotein nitrogen levels of the blood which have been seen are those associated with some form of renal failure. The degenerative types of Bright's disease characterized by profuse albuminuria, renal edema, serum protein reduction, without

hematuria or significant hypertension, have shown an elevation of non-protein nitrogen in the blood only in the terminal stages when renal failure supervenes, and usually in the presence of intercurrent infections which are likely to terminate the course of such a disease. The patient with degenerative Bright's disease has a tubular lesion and the difficulty is in regard to the water balance. The glomeruli are apt to be relatively normal and consequently no great difficulty is experienced in excreting the nitrogenous waste, provided an adequate urinary volume is arranged for. Such patients tolerate diets with high protein content well and may show positive nitrogen balances over a long period of time on a high protein intake, indicating a protein deficit undoubtedly caused by the albuminuria. As a matter of fact, the high protein diet increases the excretion of urea somewhat and this in itself tends to increase diuresis and lessen the edema. The administration of sufficient protein to cover the usual metabolic requirement, plus an additional amount to replace the loss of proteins as albumin in the urine, may be safely given without any danger of increasing the nitrogen in the blood. Even a considerable amount of additional protein may be given without danger because it is used for the restoration of wasted tissues. The high protein feedings which have been advised in this condition therefore have a rational basis, but it is often difficult to make these patients take diets containing 100 to 150 grams of protein daily. In these patients the actual administration of urea itself as a diuretic is often extremely beneficial and as much as 40 to 80 grams a day may be given without an increase of nonprotein nitrogen in the blood. Some transitory increase, indeed, may be noted but it is only by virtue of the fact that the urea does accumulate in the body to a certain extent that it gains its diuretic effect. It should, of course, be used with caution in the presence of azotemia and particularly if diuresis does not develop.

Accumulations of nitrogenous wastes are most apt to occur in those cases of Bright's disease characterized by persistent hematuria, hypertension, albuminuric retinitis, and eventually by the uremic syndrome. It is interesting to note that those patients who might be described as having a nephrotic type of chronic hemorrhagic Bright's disease characterized by edema and gross albuminuria are less likely to terminate in a state of uremia. Temporary elevations of the nonprotein nitrogen level of the blood are, of course, common in the acute phases of Bright's disease and may subside entirely with recovery of the renal state. Consequently, the actual level of the nonprotein nitrogen is of little prognostic significance in Bright's disease but much more important is the question of the direction which it is taking. In its inception, at least, acute hemorrhagic Bright's disease is often only a local expression of a general infection and this latter, by increasing nitrogen metabolism, may play



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a considerable part in determining the extent of the accumulation of nonprotein nitrogen in the blood. The nonprotein nitrogen may rise in the presence of a comparatively high concentration of nitrogen in the urine and in negative nitrogen balance. The increase in these cases is usually due to a summation of the effects of impairment of renal function, insufficient urinary output, and increased nitrogen metabolism. In acute nephritis at times the rapid delivery of edema may result in a marked elevation of nonprotein nitrogen in the blood, the explanation of which is that the kidney apparently excretes the water much more readily than it does the nitrogenous waste which thus tends to be concentrated in the blood stream.

The highest elevations of nonprotein nitrogen noted have been seen in the end stages of chronic hemorrhagic Bright's disease. Retention occurs only when the renal function falls to a urea clearance value of approximately 20 per cent, although some elevation of the nonprotein nitrogen level of the blood may be noted with urea clearance values of 50 per cent or below. One patient seen recently at the Clinic was reported as showing a nonprotein nitrogen content of almost 600 mg. per 100 cc. Such elevations of the nitrogenous waste in chronic hemorrhagic Bright's disease are, of course, very serious unless there is some complicating factor such as heart failure which may help explain the rise as being due to some disturbance of renal circulation and not to an essential failure of the excretory function of the kidney. The fever which accompanies chronic hemorrhagic Bright's disease may aggravate the situation by causing a toxic destruction of body protein, but undoubtedly the biggest factor is the failure of the renal epithelium to secrete urea normally. By far the greater fraction of the elevation of the nitrogen in the blood is to be found in the urea portion. Uric acid, creatinine, and undetermined nitrogen are also elevated to a lesser degree, whereas amino acids and ammonia nitrogen are never significantly increased.

With the development of clinical uremia, some elevation of the nitrogenous waste in the blood is certain although this relationship to the clinical condition is extremely variable. Symptoms of uremia may develop while the nonprotein nitrogen in the blood is normal or only just above the normal limit and on the other hand may fail to appear even when the nonprotein nitrogen is extremely high. This variability is to be expected from the fact that neither urea nor any other known constituent of the nonprotein nitrogen appears to be responsible for the production of clinical uremia. As noted above, nonprotein nitrogen values as high as 300 mg. per 100 cc. have been noted in the blood of patients with longstanding pyloric obstruction without any symptoms of uremia and values almost as high have been noted in severe diarrhea.

Bollman and Mann<sup>5</sup>, by implanting the ureters of dogs into the intestine so that the excretion of nitrogen in the urine was continually reabsorbed from the gut, have caused chronic increases of nitrogen in the blood urea amounting to more than 300 mg. per 100 cc. without the appearance of any symptoms of uremia.

Despite these apparent contradictions, the appearance of blood non-protein nitrogen levels of 150 mg. or over are suggestive that uremia is not far distant, provided that elevation is due to disturbance of renal function. In the terminal stages of uremia the nonprotein nitrogen level of the blood may rise at tremendous rates, due partially to the fact that these patients become markedly dehydrated because of the inability to retain fluids and develop partial starvation. Further than this, the motor irritability and activity so characteristic of the state of uremia must increase caloric requirements and will increase protein catabolism when the ability to take fat and carbohydrate is limited.

In the arteriosclerotic kidney, accumulation of nitrogenous waste is less often seen because of the fact that the renal lesion is only part of a generalized vascular disease and renal failure is likely to be prevented by termination from cerebral vascular accident or myocardial failure. When renal failure does occur in this condition, the metabolic and chemical disturbances are indistinguishable from those found in chronic hemorrhagic Bright's disease.

Some elevation of the nonprotein nitrogen level of the blood is frequently seen in partial obstructions of the genito-urinary tract from prostatic hypertrophy or urethral stricture. The elevated nonprotein nitrogen may develop rather suddenly and reach levels as high as 200 mg. per 100 cc. It is rather characteristic of these increases that they are not accompanied by symptoms of uremia and with the relief of obstruction the normal level is quickly restored unless there has been underlying renal damage. Mass destruction of kidney substance from renal tumors, tuberculosis, pyelonephritis, hydronephrosis, pyonephrosis, and renal vessel thrombosis may result in markedly elevated non-protein nitrogen levels of blood. Generally it is regarded that such an increase is suggestive of bilateral renal disease although cases have been reported in which the pathology was apparently unilateral. Such instances have usually been seen where one kidney was the seat of an infectious process and presumably the increased protein catabolism has overloaded the remaining kidney for the time being. It is frequently difficult to be certain that the remaining kidney is normal. Congenital polycystic kidney is a bilateral condition which is frequently responsible for a chronic type of increased nonprotein nitrogen level which may persist over years, during which the patient may carry on a normal activity. The renal reserve in such patients, however, is extremely small and a sudden excess strain upon the kidney, such as occurs with

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a simple respiratory infection, may be sufficient to precipitate a marked further elevation of nitrogenous waste and death from renal failure. Blood urea levels of more than 100 mg. per 100 cc. certainly suggest that the patient is a poor operative risk at that time and indicates the necessity for conservative measures to relieve the obstruction or increase urinary output in order to secure more normal levels before radical operation is undertaken. Single determinations of the level of blood urea are not in themselves so significant but rather repeated checks should be made to determine its direction, particularly in relation to therapy.

Studies of the total urinary nitrogen are of great value in such conditions. If the excretion of the urinary nitrogen is greater than 8 grams per liter, it is presumptive evidence that the kidneys are damaged so little that provision of adequate volume of urine and reduction of protein catabolism may be expected to effect a considerable reduction in nonprotein nitrogen of the blood in these obstructive lesions as in the urea fraction when the urea may rise from its usual 50 per cent to comprise from 80 to 90 per cent of the total nitrogen of the blood. Uric acids and creatinine are less consistently affected while the undetermined nitrogen rises but to a lesser extent than urea. The ammonia and amino acid fractions alone appear to be entirely unaffected.

The marked elevation of one small fraction of the nonprotein nitrogen, namely uric acid, in acute attacks of gout is of considerable interest. The elevation of uric acid may occur without any appreciable elevation of the other fractions and there would appear to be some disturbance of the specific mechanism for metabolism of this constituent. Elevation of the total nonprotein nitrogen may be seen with acute attacks of gout but can be explained on the basis of the increased protein catabolism of the acute attack as well as the underlying renal lesion which so often occurs in these patients.

In summary it is apparent that the level of the blood nonprotein nitrogen at any given time is determined by the relationship of several different factors. These fall naturally into two important groups, namely, those which favor the increased production of nitrogenous wastes, chiefly protein catabolism, and those which favor their retention within the body, chiefly renal inefficiency. The largest fraction of nonprotein nitrogen in the blood is that contained in the urea and the greatest fluctuations are found in this constituent. The level of blood urea is usually used as an index of the relationship between the two main fractions of the nonprotein nitrogen. Certain physiological variations of minor degree are noted. Major variations are of serious import and call for immediate therapy which depends upon the associated disturbances but mainly is concurred with a reduction of protein catabolism or increased urinary flow.

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