An examination of the blood revealed changes usually associated with anaphylactic shock.

In some cases urticaria follows the ingestion of or contact with a substance to which the patient has not been previously exposed; therefore anaphylaxis does not always serve to explain the reaction, and we have to fall back on the term "sensitization"—the inexplicable predisposition or idiosyncrasy to react to stimuli which have no effect on a normal individual. There is evidence to show that the antigen may be ingested, inhaled, or absorbed through the skin, and yet produce the same results. Also that the so-called sensitiveness exists in the serum, for Prausnitz and Küstner⁷ injected the serums of hypersensitive patients into the skin of normal individuals and found that the site of the injection was temporarily sensitized to the same substance. This was confirmed by A. Walzer and M. Walzer,⁸ who noted that the serum possessed this activity for some months after it was withdrawn from the sensitized person. The susceptibility may be transmitted by a female guinea-pig to her offspring (Rosenau⁹). Another observation which has an important bearing on the treatment is that when once acquired the sensitiveness to a particular antigen appears to be followed by sensitiveness to other antigens.

May this reaction of the skin be of some protective significance? This point is raised by Memmesheimer¹⁰ in relationship to eczema, but there is little to support this hypothesis. The histology of the wheal certainly shows that cell damage takes place, and therefore cell products escape into the general circulation. We know that immunity follows an attack of measles and scarlet fever, diseases in which the skin is particularly affected; but we are equally cognizant of the fact that in many other diseases involving extensive areas of skin no protection is acquired.

Etiology.

Although the conception of the biological changes associated with an attack of urticaria has changed considerably in later years, it is interesting to note that the dermatologists of the middle of the last century fully recognized the diversity of the causes of the reaction. In every textbook, ancient and modern, there is a long list of both external and internal causes, and almost every observer is able to add to the list. Hebra noted that the introduction of a uterine sound produced a profuse urticarial rash in one of his patients. Crocker¹¹ quotes a case in which a ring at the front door would determine an attack. We know that it may mask a scabies infection; that it follows the ingestion of some particular food or drug. Furthermore, it may be one of the earliest signs of a grave disease such as leukaemia or diabetes; also, it may be associated with focal sepsis. The latter coincidence has been so frequently demonstrated in recent years that it must be accepted. My own view is that focal sepsis plays a far greater role in the causation of chronic urticaria than food protein, and that in the past it has been assumed too readily that urticaria is the outward manifestation of food poisons.

As the chance of successful treatment largely depends on the detection of the cause, it is essential that a case of urticaria should be approached with the greatest circumspection, and also with the knowledge that there is no specific remedy. A detailed history will be required; the skin will need careful inspection to exclude the possibility of local irritants. Protein sensitization tests must be considered, although these have not given the assistance that was anticipated from them. Each system will require examination, for none is above suspicion. The key to the mystery may be the examination of the blood. In a recent article F. R. Menegh¹² claims that disease of the biliary tract was an etiological factor in 50 per cent. of his cases. A high incidence of urticaria has been described in patients with syphilis, and I have met with this coincidence on several occasions, but antispasmodic treatment has not prevented the recurrence of the wheals.

It is sufficiently obvious that there are innumerable possibilities to be considered, and that the physician who successfully detects the offending abnormality has good reason to congratulate himself. That trauma plays an

important part as an exciting cause was demonstrated as long ago as 1888 by Jaquet, who found that when a limb of a patient suffering from generalized urticaria was protected the wheals did not arise on the skin of that limb.

Desensitization.

Should the offending antigen be detected, desensitization may be attempted by giving minute, increasing doses until tolerance is established. On the assumption that urticaria is a manifestation of the anaphylactic state French dermatologists have recently advocated the ingestion of 0.5 gram of peptone one hour before each meal.

Empirical Remedies.

Calcium salts have had a long innings, but in my experience the results have been singularly disappointing, and in my opinion confidence in the supposed virtues of this drug have many times been responsible for an inadequate examination of patients. Urticaria has been noted in hypothyroidism; therefore thyroid extract has recently been prescribed as a remedy; one author, indeed, proclaims it as a specific. I do not go so far with him, but believe, in the unhappy event of the actual cause not being ascertained, that thyroid extract is worthy of a trial. Papular urticaria is influenced neither by dieting nor drugs, but, as already mentioned, the patient obtains a respite if he be removed from his own environment. True, the rash often recurs when the patient returns home, but I have noted a permanent benefit in a number of instances, and recommend a trial when practicable.

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BIOCHEMICAL INVESTIGATIONS IN ALLERGIC CONDITIONS.*

BY

H. W. BARBER, M.A., M.B., F.R.C.P.,

AND

G. H. ORIEL, M.A., M.D.

OUR communication is concerned almost entirely with certain biochemical investigations carried out by one of us (G. H. O.) in what may be termed allergic conditions. The word "allergy," in the sense originally employed by von Pirquet, has a narrower significance than others have given to it, for, as Darier points out, although including all forms of acquired hypersensitiveness, it excludes inborn hypersensitiveness or idiosyncrasy. We do not, however, consider this distinction of practical importance, or, in fact, valid, and with Doerr, Zinsser, Wells, Duke, and others, we employ the term to indicate almost all forms of hypersensitiveness.

Allergy is beyond question the most important biological and medical problem that exists or ever has existed, for it represents the pathology of the reaction of man and the lower animals to their environment—to the air they breathe, the physical agents, such as light, heat, and cold, to which they are exposed, the food they eat, and the various parasitic organisms which may invade them.

Moreover, in our opinion the discussions that have arisen as to whether or not the so-called allergic conditions, such as hay fever, asthma, and urticaria, should be termed anaphylactic reactions, or whether they differ essentially from true anaphylaxis as produced in animals experimentally, or as it may occur accidentally in man, are profitless. The important fact is that many of the

* Read in a discussion on urticaria in the Section of Dermatology of the Annual Meeting of the British Medical Association, Cardiff, 1928.

symptoms to which sensitized persons are liable are identical with those seen in animals suffering from anaphylactic shock—for example, contraction of the pilo-motor muscles with erection of the hair follicles, sneezing and coughing, pruritus, urticaria, respiratory distress consequent upon the contraction of the smooth muscle of the bronchioles, and oedema of the bronchial mucous membrane, diarrhoea, diuresis, and epileptiform convulsions.

The following list includes the majority of conditions which are certainly, or in some instances probably, of allergic origin:

Cutaneous.—Urticaria; true infantile eczema; certain forms of eczema occurring after infancy; certain forms of pruritus; prurigo of the Besnier type; prurigo of the Hebra type; prurigo of the simple type; prurigo nodularis; urticaria papulosa (lichen urticatus, strophulus); ichthyosis; light sensitization of the adult type; dermatitis herpetiformis (probably).

Subcutaneous.—Angioneurotic oedema.

Respiratory Tract.—Paroxysmal rhinitis, of which hay fever is one of the commonest examples; asthma.

Gastro-intestinal Tract.—Certain forms of vomiting and diarrhoea.

Nervous System.—Migraine; epilepsy (probably).

Articular System.—Paroxysmal hydrarthrosis.

This list, although it may appear formidable, is doubtless incomplete. Freeman¹ includes functional albuminuria, and tentatively dermatographia, paroxysmal colitis, and white leg.

The literature of allergic conditions, from both the clinical and the pathological standpoint, is so vast that we have made no attempt to review it. We shall merely summarize our own observations and refer to a few communications of other workers that bear upon them.

It may be of interest to record how we came to investigate the biochemistry of allergic manifestations. It seems clear that in cases of what may be called the ichthyosis-asthma-hay fever-eczema-prurigo-urticaria-migraine syndrome, in which there is almost invariably a strong family history of one or other of these various manifestations, there must be some inborn metabolic kink—comparable to Garrod's "inborn errors of metabolism"—which predisposes the affected person to becoming sensitized to various proteins.

The inherited "sensitizability" of Cooke and van der Veer must have some metabolic explanation, and in persons, previously normal, who develop the allergic state it was thought the same metabolic error would be found. Now the view has long been held, not only by certain clinicians but also by laboratory workers, that both in experimental anaphylaxis and in allergic conditions, such as asthma and urticaria, the essential factor is what may be vaguely termed "hepatic insufficiency." One need only refer in this connexion to the writings of Widal and his co-workers, of Manwaring, and, from the clinical standpoint, to the views of Moncorgé and others, on the pathogenesis of asthma.

One of us (G. H. O.), working on oedema from the biochemical point of view, had discovered a phenomenon in the urine, which may be termed the "ether reaction," in certain cases of cardiac failure. This reaction will be described and discussed later. On testing the urine of normal controls, he found that one of his laboratory assistants gave a strongly positive test, and on questioning the man, he learnt that he was healthy except that he suffered from urticaria. It was then found that other urticarial subjects also gave positive tests. The question therefore was: What is the connexion between cardiac failure with oedema and urticaria? It occurred to us that the most probable explanation was either that in both conditions there is some degree of hepatic insufficiency, of which the ether reaction in the urine is an indication, or that some factor concerned with the production of tissue oedema was common to both. It was then decided to test the urines of persons with allergic symptoms other than urticaria, and positive reactions were at once found in cases of prurigo of the Besnier type, with or without asthma, in asthma without cutaneous symptoms, in urticaria papulosa, in angioneurotic oedema, in certain cases of prurigo of the simple type, in infantile eczema, and in

migraine. Numerous normal controls were, of course, also tested. It was further found that the reaction was strongly positive in obstructive jaundice, in cirrhosis of the liver, and in cases of toxic jaundice—for example, from salvarsan or acute infections—thus lending, perhaps, additional support to the view that the reaction was an indication of hepatic insufficiency.

Assuming, therefore, that these allergic conditions were, at any rate in some cases, associated with functional hepatic insufficiency, and that such insufficiency concerned protein metabolism (cf. the proteopexic function of the liver of Widal) the next step was to estimate the amino-acid content of the blood in patients with allergic manifestations and in normal controls.

The method used was that of Folin, as described in *Recent Advances in Medicine* by Beaumont and Dodds.

AMINO-ACID CONTENT OF THE BLOOD.

It would appear from our own investigations and those of others that the average normal figure for the amino-acid content of the blood is from 4.0 to 6.5 mg. per 100 c.cm., the latter figure being distinctly a "high normal." In order to determine the effect of a meal containing plenty of protein, what may be called "protein-tolerance tests" were performed in normal subjects and in those with allergic symptoms. A determination of the amino-acid content of the blood was made before breakfast or several hours after a meal, and a mixed meal containing various proteins was then given, and estimations were made one, two, and three hours afterwards—for example:

G. H. O., normal subject: before breakfast 3.7 mg. per 100 c.cm.; one hour after breakfast 4.7 mg., which figure remained constant two and three hours afterwards.

N., normal subject: 5.0 mg. before a meal; 5.8 mg. afterwards.

K. R., normal: 4.0 mg. before; 5.6 mg. afterwards.

A., a case of dermatographism and urticaria: 5.0 mg. before a meal; one hour afterwards 5.5 mg.; two hours afterwards 6.2 mg., when there was slight urticaria; three hours afterwards 5.8 mg., when the urticaria had disappeared.

W., a case of asthma and prurigo: fasting 7.0 mg.; one hour after meal 7.2 mg.; two hours after 7.4 mg.; three hours after 7.2. It will thus be seen that there is a slight rise in the amino-acid content of the blood after a protein meal both in normal persons and in others.

A very large number of estimations have been carried out in patients with allergic manifestations, the majority of cases investigated being classical examples of the ichthyosis-asthma-hay fever-eczema-prurigo-urticaria-migraine syndrome, in a considerable proportion of which more than one of these various symptoms were combined. In this group, which for brevity's sake we will term the asthma-prurigo group, a high amino-acid content of the blood was found to be constant in untreated cases; but it is necessary to make this reservation—that the patients as a rule were seen when one or other of their symptoms, usually the prurigo, was active. After dietetic and other treatment, and probably also during the remissions, that so often and so inexplicably occur in these patients, normal figures may be obtained. For example:

W. was a typical example of the group; he gave a family history of asthma and migraine, suffered himself from infantile eczema, which was later followed by asthma and prurigo of the Besnier type with lichenification, involving chiefly the antecubital fossae, the popliteal spaces, the dorsal surfaces of the wrists and hands, the circumoral and frontal regions. He is an ichthyotic. When seen early in December, 1927, he was having moderately severe asthmatic attacks about three times a week and nocturnal exacerbations of itching. His lips were bluish in colour, and rhonchi were audible in the chest. The blood, drawn in the afternoon—a quiescent period—gave an amino-acid content of 7.0 mg. per 100 c.cm. He was ordered a vegetarian diet except that he was told to eat some lightly cooked liver, if possible, daily, and given sal volatile to take thrice daily. In a fortnight he returned transformed in appearance; he was entirely free from asthma, had little or no itching, and his lips were now pink. The amino-acid figure was 5.8—that is, normal. Treatment was suspended; he returned in January, having kept very well except for slight asthma and itching at night-time. His amino-acid figure then was 7.0. Early in March he came again, having had a severe relapse following a gastro-intestinal upset; he was having asthma every night, with intense itching; his lips had become blue again, and his chest was full of rhonchi. The amino-acid figure was 9.3. Treatment was again ordered, and he returned in a fortnight much improved. The amino-acid content had fallen to 7.0.

It is our impression that in cases of Besnier's prurigo, with or without asthma, the amino-acid content of the

blood tends to be high even during periods of comparative freedom from itching. Thus:

S. C., a man aged 42; family history of eczema; ichthyosis on the father's side. Had infantile eczema. Asthma began at the age of 2 years. Asthma and irritation of the skin were provoked by contact with horses and cows; also asthma with catarrhal infections. Severe urticaria and angioneurotic oedema from Brazil-nut, which once nearly caused death from oedema of the glottis, when taken accidentally. Has ichthyosis and prurigo of the Besnier type in antecubital fossae, popliteal spaces, wrists, and face. Cutaneous tests: Horse +++; cattle +; dog +; sheep +; Brazil-nut +++. During a period of almost complete absence of symptoms nevertheless had an amino-acid figure of 9.8.

V., a little boy with Besnier's prurigo; formerly infantile eczema and asthma; at a time when the prurigo was slight had an amino-acid figure of 8.2.

P. B., a little girl with asthma, hay fever, horse sensitiveness, eczema, prurigo, and urticaria. Seen during one of her best periods, when she was having no asthma and only slight itching; amino-acid 9.3.

Of forty-one patients belonging to this group, in nearly all of whom there was a combination of asthma or hay fever with prurigo of the Besnier type, and several of whom were ichthyotics, the average figure for the amino-acid content of the blood was 8.8. The highest figure in this series was 10.7, the lowest 7.0, but examinations made in a few asthmatic patients during an actual attack gave much higher readings—for example, 17.5 in one case, 18.6 in another. These figures have not been included in the above series.

In simple cases of urticaria and of asthma without prurigo it would appear that in the intervals between the attacks the amino-acid figure may be normal, or nearly so, but it rises rapidly during the paroxysms. Thus the asthmatic who in an attack gave the above figure of 18.6 gave in a quiescent period only 6.8, and the patient with 17.5 in the attack at another examination gave 8.0. One case of urticaria gave 6.4, rising during an attack to 11.8; another 5.0, rising to 7.4 and 9.3. Some of our urticarial patients with nocturnal attacks have given figures well within normal limits during the daytime; in others, however, they have been raised even at times when no eruption was present. A patient with angioneurotic oedema gave 6.0 in an interval between attacks, rising to 8.2 during one.

To sum up, the conclusions at which we have arrived from investigations made in a large number of patients are as follows:

1. During the acute paroxysms of allergic manifestations the amino-acid content of the blood is very markedly raised.
2. In cases of prurigo of the Besnier type, in which asthma, hay fever, and ichthyosis were often also present, high figures were usually obtained even during periods of comparative freedom from symptoms. The figure rose still higher during the paroxysms of itching.
3. In cases of simple urticaria or of angioneurotic oedema, and of asthma without prurigo, the figure may be normal or nearly so in the quiescent stage, but is constantly raised, sometimes to an extraordinary extent, during the attacks.

A raised amino-acid content of the blood has also been found in cases of light-sensitization of the adult type, in four cases of dermatitis herpetiformis, in some cases of simple prurigo occurring for the first time in adult life, in prurigo nodularis (three cases), in certain cases of eczema of the "gouty" type associated with a high blood pressure, in a case of dermatitis exfoliativa of unknown cause, in cases of salvarsan poisoning with jaundice, in one patient with cirrhosis of the liver, and in a case of intermittent hydrarthrosis associated with psoriasis. On the other hand, normal figures have been obtained in uncomplicated psoriasis, in one case of cirrhosis of the liver, in one case of toxic jaundice following tonsillectomy, in a case of sarcoid, in one of alopecia areata, and in a case of generalized eczematous dermatitis apparently due to septic absorption. In healthy normal subjects the figures are remarkably constant.

In experimental anaphylactic shock Hisanobu found a rise in the blood of total non-protein nitrogen and of amino-nitrogen.

With regard to the other non-protein nitrogenous substances—for example, urea, uric acid, and creatinine—we have not as yet estimated them in the blood in a sufficient

number of cases to enable us to draw any definite conclusions, but it would appear that during the acute paroxysms their quantity is raised. At all events, they are excreted in increased amounts in the urine at and during the period immediately following the paroxysms, and the output of creatinine would seem to be particularly high in cases of urticaria. Such an increase of non-protein nitrogen excretion has also been observed by Longcope and Rackemann to follow attacks of acute urticaria.

As to the significance of a raised amino-acid content of the blood we can say nothing. It is possible that it may be at any rate partly accounted for by the presence in the blood of toxic amines, of the histamine type, which are known to produce symptoms comparable to anaphylactic shock, and the various allergic manifestations. On the other hand, it may merely be an indication of the disturbance of endogenous protein metabolism that obtains in anaphylactic shock, and in the proteose intoxication which, as Whipple and others have shown, occurs in experimental intestinal obstruction, and in which the non-protein nitrogen in the blood is greatly raised. That the endogenous protein metabolism is excessive in the acute stage of allergic states is shown by the increased creatinine excretion that follows them.

CHLORIDES.

In the early period of our work the importance of the chloride content of the blood and of the urinary excretion of chloride was not realized. Of late, however, one of us (G. H. O.) has investigated cases of various diseases from this point of view, with significant results.

In serum disease von Pirquet and Schick showed that there was a relative increase in weight which they considered due to retention of fluid. Rackemann, Longcope, and Peters demonstrated that there is, during the active stage of serum disease, a marked but transient retention of chlorides and water, associated sometimes with a slight albuminuria and cylindruria, and occasionally with an impairment of the excretion of phenolsulphonephthalein by the kidneys. They stated that in patients with oedema and a gain in weight during serum sickness the plasma chlorides were below normal. Rackemann and Longcope also investigated six cases of urticaria both during and after attacks. In one patient sensitive to beef and sheep protein the attack of urticaria was associated with a rise in blood urea, a decrease in the phthalein output, diminished excretion of urine, and almost complete suppression of chloride and nitrogen excretion. During the period immediately after recovery the nitrogen and chloride excretions were excessive, and the blood urea, the phthalein output, and the water exchange returned to normal. During this period there was a loss of almost 8 lb. in weight. These results, as will be seen, correspond almost exactly with our own findings in allergic diseases.

In infantile eczema Lust and Lederer found at times a considerable increase in the water content of the blood as compared with normal infants, and wide and rapidly occurring fluctuations of the water content were characteristic. These fluctuations appeared to depend on alterations in the metabolism of mineral salts. Freund found that eczematous infants showed a much greater retention of chloride than non-eczematous infants on the same diet. This retention of chloride was coincident with a rapid gain in weight due to a simultaneous water retention. Meyer found that if eczematous infants were underfed there was a much greater excretion of mineral salts than in normal infants on the same diet.

In considering the chloride content of the blood a distinction must be drawn between the serum content and the whole blood content. The chloride content of a given volume of serum is greater than that of the same volume of whole blood, showing that normally the serum chloride exceeds that in the corpuscles. The normal readings are fairly constant: a series of estimations in normal controls gave figures varying from 570 to 585 mg. per 100 c.cm. of serum, and 454 to 495 mg. per 100 c.cm. of whole blood. These may probably be taken to represent the normal limits. The chloride content is estimated as the chlorine ion, and the result expressed in terms of sodium chloride, although the actual combination of the chlorine ion varies in the serum

and the red cell; it is probably present as sodium chloride in the serum and potassium chloride in the red cell.

Now it would appear that in acute and chronic allergic manifestations the whole blood chlorides are markedly diminished, whereas the serum chlorides may remain about normal—that is, there is a reduction of the corpuscle content of chloride. As with the increase of the blood amino-acid content, we have found that this reduction of whole-blood chloride is most constantly found in the asthma-prurigo group, and, like it, varies with the exacerbation or remission of the symptoms. In simple urticaria the chloride reduction takes place, like the increase in blood amino-acid, during the attacks, and usually returns to normal in the intervals. Thus:

Disease.	Amino-acid Content of Blood. Mg. per 100 c.cm.	Serum NaCl. Mg. per 100 c.cm.	Whole Blood NaCl. Mg. per 100 c.cm.
Normal	4.0-6.5	570-585	454-495
1. Asthma, ichthyosis, prurigo...	7.0-9.3	577	346
2. " " " ...	7.0-7.7	561	363
3. " " " ...	7.0	627	396
4. " " " ...	7.0	561	322
5. " " " ...	7.0	610	380
6. " " " ...	7.0		380
7. " " " ...	8.7		305
8. " " " ...	8.7		430
9. " " " ...	7.0		363
10. Asthma, ichthyosis, prurigo, urticaria	10.0		412
11. Angioneurotic oedema, urticaria (quiescent stage)	7.0		396
12. Asthma, ichthyosis, prurigo, urticaria	9.3		412
13. Asthma	7.0	577	363

One case of severe prurigo of the Besnier type associated with occasional attacks of asthma was investigated at various times.

On April 24th, 1928, after having been for some time on a vegetarian diet, the patient was fairly free from itching; amino-acid 5.4 mg. per 100 c.cm.; serum NaCl 577 mg. per 100 c.cm.; whole blood NaCl 396 mg. per 100 c.cm. Given sal volatile, potassium bicarbonate, and urea. On May 1st was much better. Serum NaCl 610 mg. per 100 c.cm.; whole blood NaCl 430 mg. per 100 c.cm. On May 7th patient had a relapse with severe itching and asthma following a catarrhal infection with some pyrexia. Amino-acid 7.0 mg. per 100 c.cm.; serum NaCl 561 mg. per 100 c.cm.; whole blood NaCl 363 mg. per 100 c.cm. On May 13th the asthma had gone, but there was still some itching. Amino-acid 7.7 mg. per 100 c.cm.; whole blood NaCl 396 mg. per 100 c.cm.

A case of angioneurotic oedema gave the following figures:

	Before Attack.	During Attack.
Amino-acid	5.8 mg. per 100 c.cm.	8.2 mg. per 100 c.cm.
NaCl (whole blood) ...	480 " "	396 " "
NaCl (serum)	580 " "	577 " "

THE URINE.

A study of the urine has proved of very great interest and importance in allergic states, and it is no exaggeration to say that not only can we now deduce from a given specimen, taken from a person with allergic symptoms, whether it was passed at the onset or during the paroxysm or in the period following it, but we can also predict the urinary findings according to the condition of the patient at a given time.

There are two phenomena which we believe to be almost if not quite constant in persons with allergic symptoms at certain times during the periods of active manifestations—namely, the ether reaction, already referred to, and the deposition of urates in the urine on cooling. These will be discussed later.

Before considering the urinary findings in detail it is advisable to summarize what we have found to occur in the cycle of events that takes place in all the acute allergic states so far investigated—for example, an attack of asthma, urticaria, angioneurotic oedema, or migraine, and in the paroxysms of itching that occur periodically in prurigo and infantile eczema. In the period just preceding and during the paroxysms we find:

Blood:

1. The amino-acid content rises.
2. The uric acid and creatinine are also apparently increased.
3. The chloride content of the whole blood—chiefly of the corpuscles—falls.

Urine:

1. Free acidity rises.
2. Urates are often deposited when the urine cools.
3. Diminished water excretion, so that the specific gravity is usually high.
4. Retention of chlorides.
5. Ether reaction strongly positive.
6. Ammonia excretion rises and the ratio of free acid to ammonia is altered.
7. Excretion of amino-acid, creatinine, and uric acid begins to rise.

In the period following the subsidence of the paroxysm we find:

Blood:

1. The amino-acid content falls again.
2. The uric acid and creatinine also diminish.
3. The chloride content of the whole blood rises again.

Urine:

1. The free acidity rapidly and progressively falls, and the urine tends to become neutral and finally alkaline, sometimes strongly so.
2. Increased excretion of water, so that the volume is raised and the specific gravity falls (post-paroxysmal diuresis).
3. The excretion of chlorides is increased.
4. The ether reaction diminishes and may entirely disappear.
5. The excretion of ammonia begins to fall, but it, so to speak, lags behind the diminishing excretion of acid so that the ratio of free acid to ammonia is still further altered.
6. Excretion of amino-acid, creatinine, and uric acid gradually falls.

The Precipitation of Urates.

The precipitation of urates in the urine on cooling is a phenomenon that has not, in our opinion, received sufficient attention from clinicians. It is usually taught that such a precipitation when the urine cools depends on (1) the concentration, (2) acidity. As a matter of fact these factors are of relatively minor importance. We have seen a heavy deposit of urates in a urine with a quite low free acidity and a specific gravity of only 1012. The following remarks are taken almost *in extenso* from an article on renal calculi by Jacob Rosenbloom in *Endocrinology and Metabolism* (D. Appleton and Co., New York and London, 1924, vol. 4, pp. 465-467).

Temperature, as is well known, has a great influence on the solubility of acid sodium urate. It may often be observed that a precipitate which disappears on boiling the urine does not reappear on cooling, and that the urine remains clear for hours or even days. Some change must therefore have taken place in the urine by heating. Decomposition of uric acid is not in question; decrease of acidity from the small loss of CO₂ cannot account for the change. One can even make the urine more strongly acid after heating without hastening the formation of a precipitate. This phenomenon of change in solubility may be found at times in urines which give a dense uric acid precipitate on acidification. If one adds the same amount of acid to the heated urine the precipitation may fail or come later.

It can be shown that, by boiling, a change in the solubility state of the colloid is produced. Lichtwitz examined fifty-seven such urines for their colloid conditions. The gold count was made before and after boiling, and the time noted that the sediment remained in solution. The gold count increased from two to ten times—that is, the urine colloids were in a state of precipitation in these urines, and became reversible through boiling, as gelatin by warming goes into a finer separation. In eighteen urines that precipitated on cooling the gold count was the same before as after boiling—that is, the colloid which these urines contained was in an irreversible precipitation state. Such urines may be without defence action for colloidal gold solutions. Lichtwitz observed a patient who passed urine for four weeks without a gold count with abundant uric acid sediment; only on one day was the urine clear and acted protectively on the gold solution.

These observations show that the solubility of the uric acid and its salts depends on the colloid state of the urine. The concentration is of subsidiary importance, for precipitation may occur with quite normal amounts, while abnormal amounts may remain in solution. Other conditions being the same, a sediment occurs naturally more readily in concentrated urine. The reaction is of significance merely in so far that precipitation only occurs in acid urines. If occasionally the reaction is neutral, it is due to the fact that in crystallization hydrogen ions have left the solution and thereby reduced its acidity. At any rate, in very strongly acid urines the uric acid may remain dissolved.

The dominant factor for the solubility is the state of the urine colloids. It may be here remarked that, since the precipitation of urates does not depend on the uric acid itself, such precipitation does not in any way indicate the "uric acid diathesis." Brugsch and Schittenhelm have pointed out that whereas true gout is extremely rare in childhood, uric acid stone is most frequent, and the majority of cases of urate stone diathesis occur without true gout.

Now although the precipitation of urates may be found in the urines of apparently normal healthy people, it is, in our experience, comparatively rare, and we believe that, apart, perhaps, from its occurrence after excessive sweating, it is an indication, even in persons organically sound, of at any rate a temporary functional metabolic disturbance. One of us (H. W. B.) makes a rule to examine an early morning specimen of urine of nearly every patient he sees in private practice, and urates are more commonly deposited in the night or early morning urine than at other times; nevertheless, except in patients with allergic symptoms, it is rare to see a specimen with uratic sediment. Even in patients with acute seborrhoeic manifestations, in whom the urine is usually excessively acid, such sediment is very uncommon.

In allergic diseases, however, it is so frequently met with as to be almost constant at some period in the twenty-four hours, at least during the phase of active manifestations. In infantile eczema, urticaria, and in the asthma-prurigo syndrome, for example, an inquiry as to whether a reddish sediment has been noticed in the urine on cooling will almost invariably be met with an affirmative reply.

It would seem, therefore, that in allergic diseases there is an alteration in the colloidal state of the urine which predisposes to the deposition of urates, and one naturally asks whether this phenomenon is not a reflexion in the urine of the *crise hémoclasique*, or *colloïdo-clasique* in the blood.

The Ether Reaction.

This reaction, as has been said, was first observed by one of us (G. H. O.) in cases of cardiac failure with oedema. The test is performed as follows: To a few cubic centimetres of urine are added first a little of a 25 per cent. solution of sulphuric acid, and then sufficient ether to form a layer above the urine about half an inch in depth. The mixture is then thoroughly shaken, with the thumb over the mouth of the test tube, and allowed to stand. The layer of ether becomes frothy, but, if the reaction be positive, the froth in its lower part becomes viscous and opaque, like melted wax, after ten minutes or so. In strongly positive tests the tube of urine can then be inverted without spilling. The degree of positiveness is measured by the depth of the waxy scum beneath the superficial froth, and we would here emphasize that the test is one of degree only, because a slight reaction—that is, the formation of a narrow band of opaque scum—is frequently found in apparently normal people. For this reason we do not wish to exaggerate the importance of this reaction; nevertheless it is one of great interest, and deserves further study.

Microscopically the viscid scum is found to consist of finely divided globules. When the ether is evaporated there remains a little urine. Chemical analysis has thrown no light on the phenomenon, the various substances identified in the scum being normal constituents of urine, such as hippuric acid. Presumably, therefore, the reaction merely depends on reduction of surface tension. This is supported,

perhaps, by the fact that it is well seen in jaundiced urines.

As far as our observations go the reaction is always strongly positive during the acute phase of allergic manifestations, but may disappear during the period of quiescence. We have, for example, found it very marked during the acute eruptive stage of urticaria and urticaria papulosa, though sometimes practically absent between the outbreaks. In migraine—and Dr. Moreland McCrea has confirmed this—it is positive during the attacks, but may be negative at other times. In infantile eczema and the asthma-prurigo syndrome, it may be well marked in practically every specimen of urine examined, but is always most intense during the paroxysms of itching.

We have also found it in serum sickness, in hepatic disease, in acute febrile infections such as pneumonia, and in certain cases of active tuberculosis; and we have seen it strongly positive in some cases of acute toxic eruptions from food poisoning, and in generalized eczemas due apparently to sensitization to external irritants.

It would seem likely that there is a connexion between this reaction and the deposition of urates, both being probably dependent on an alteration in the colloid state of the urine, and it may be of significance that Kopoczowski and Vakram have shown that sodium oleate suppresses anaphylactic shock in sensitized animals, as also do saponin, sodium taurocholate, and sodium glycocholate, presumably owing to their power of reducing surface tension in the plasma.

Urinary Acidity and Concentration.

The acidity of the urine, as already remarked in the summary of what may be called the allergic cycle, varies according to the particular phase of the cycle. In the period preceding an attack the free acidity is, if anything, raised, but as the attack proceeds and diminishes the acidity falls, and the urine tends to become neutral and sometimes strongly alkaline, with a deposit of phosphates. During the acid stage the urine is usually concentrated, there being a diminished water excretion, and very commonly deposits urates on cooling, although, as has been remarked, uratic deposits may occur in urines of only moderate acidity and comparatively low specific gravity. During the alkaline stage it is dilute, there being a diuresis, which has long been noted clinically, for example, after asthmatic attacks. A patient may, in fact, during the same period of twenty-four hours, at one time pass a strongly acid concentrated urine with a deposit of urates and at another a highly alkaline dilute urine with a deposit of phosphates.

Ammonia.—The ammonia excretion is one of the most remarkable features of the allergic state, because it does not correspond to the degree of acidity. The normal ratio between the free acid and the ammonia excretion varies from 1:0.6 to 1:1.5 according to Davis and Rixon,² 1:1 being probably the normal average, according to our own investigations.

In persons with allergic symptoms the ammonia excretion is raised, often to an extraordinary extent, and the ratio is found to be abnormal at the period of and following the paroxysm. For example, a lady with asthma and lichenified eczema of the hands gave the following figures:

Time.	Free Acid.	Ammonia.	Ratio.	Volume.	Volume per Hour.
4.15 p.m.	38.4	81.6	1:1.5	120 c.cm.	
8.0 p.m.	50.4	138.0	1:1.6	180 c.cm.	45 c.cm.
2.0 a.m.	29.4	134.0	1:3.0	210 c.cm.	35 c.cm.
5.0 a.m.	14.4	98.0	1:4.0	180 c.cm.	60 c.cm.
6.0 a.m.	8.0	95.0	1:7.0	150 c.cm.	180 c.cm.
7.0 a.m.	—8	34.0		210 c.cm.	
Total	132.6	580.6	1:2.6	1,050 c.cm.	

The asthmatic attack was nocturnal, and it will be observed that in the latter half of the night the free acid progressively diminishes until at 7 a.m. the urine is alkaline, whereas the ammonia excretion, so to speak,

lags behind, and at 6.30 a.m. a ratio of 1:7.0 is obtained. The diuresis accompanying the alkaline stage is well shown.

A boy of 18 with asthma and prurigo gave the following figures:

Day of No Attack.

Time.	Free Acid.	Ammonia.	Ratio.	Volume.	Volume per Hour.
11.20 a.m.	24.0	91.8	1:2.0	150 c.cm.	
5.15 p.m.	45.0	122.4	1:1.6	150 c.cm.	25 c.cm.
7.10 p.m.	23.0	67.3	1:1.8	90 c.cm.	45 c.cm.
5.45 a.m.	144.0	346.0	1:1.4	600 c.cm.	60 c.cm.
Total	236.0	627.5	1:1.5	990 c.cm.	

Day of Attack.

Time.	Free Acid.	Ammonia.	Ratio.	Volume.	Volume per Hour.
1.20 p.m.	16.0	122.4	1:4.5	90 c.cm.	
4.10 p.m.	7.0	65.0	1:5.4	90 c.cm.	39 c.cm.
7.0 p.m.	12.0	38.0	1:2.0	90 c.cm.	30 c.cm.
4.30 a.m.	79.2	314.0	1:3.0	660 c.cm.	66 c.cm.
9.15 a.m.	27.0	128.0	1:2.8	270 c.cm.	
Total	141	667	1:2.7	1,200 c.cm.	

The following figures were recorded in a case of angioneurotic oedema:

Time.	Free Acid.	Ammonia.	Ratio.	Volume.	Volume per Hour.
7.0 p.m.	52.8	157.0	1:1.7	330 c.cm.	
Adrenaline 8.0 p.m.					
6.0 a.m.	115.2	440.0	1:2.3	720 c.cm.	65 c.cm.
10.45 a.m.	neutral	146.0		330 c.cm.	66 c.cm.
1.45 p.m.	neutral	34.0		90 c.cm.	30 c.cm.
4.0 p.m.	-26.4	67.0		660 c.cm.	330 c.cm.
Total	142	884	1:3.6	2,130 c.cm.	

It will be noted in this case that the attack of angioneurotic oedema was already present when the investigations were begun, and that adrenaline was administered after the first specimen of urine was examined. The figures show the gradual diminution of acidity with ultimate alkalinity, although the ammonia excretion remains high, and the very marked diuresis. Moreover, it will be seen that this progression towards the alkaline side is common to both asthma and angioneurotic oedema, and cannot be explained merely by the hyperpnoea that occurs in asthma.

Urea, Creatinine, and Uric Acid.—It will thus be seen that the ammonia excretion is raised in association with the paroxysms; the other non-protein nitrogenous substances—namely, urea, creatinine, and uric acid—are also correspondingly increased.

Chlorides.—The diminution of the chloride content of the red corpuscles has already been noted. Examination of specimens of urine taken at different times during the twenty-four hours in a patient with active allergic symptoms has shown repeatedly that during the active stage there is retention of chlorides, with a consequent low excretion of them in the urine, whereas after the paroxysm the excretion rises. This chloride retention has been shown to occur by Rackemann, Longcope, and Peters in serum sickness, and by Longcope and Rackemann in cases of urticaria. It is a well-known phenomenon in pneumonia and in other acute infections, such as scarlatina and typhoid fever. Kartamitschew and Pokorwy, and d'Urbach, have

also emphasized its occurrence in pemphigus vulgaris and in dermatitis herpetiformis. In all probability it is a protective mechanism, and the experiments of Richet and others on the prevention of anaphylactic shock in animals by the previous injection of sodium chloride support this view.

CONCLUSIONS.

The points we would emphasize in the foregoing summary of some of our investigations into the metabolism of allergic conditions are as follows:

1. Certain phenomena have been demonstrated to occur with remarkable constancy in various manifestations of the allergic state; some of these have already been described in experimental anaphylaxis and in serum sickness, which is generally admitted to be truly anaphylactic in origin.

2. In the allergic state, whether it be intermittent, as in certain cases of urticaria, angioneurotic oedema, and asthma, or whether it be more or less chronic, with periodical exacerbations or remissions, as in Besnier's prurigo and infantile eczema, there can be recognized a definite cycle of events corresponding to the pre-paroxysmal stage, the actual paroxysm, and the post-paroxysmal stage. In this cycle the most striking features are:

- The rise in the amino-acid content of the blood.
- The rise in the ammonia excretion out of all proportion to the excretion of acid in the urine.
- The lowering of the corpuscle content of chloride, and the retention of chloride during the paroxysm with its subsequent excretion, as in pneumonia and other acute infections.
- The deposition of urates in the pre-paroxysmal or paroxysmal stage.
- The ether reaction during the periods of active manifestations.
- The diuresis, with decreasing acidity and sometimes marked alkalinity of the urine in the post-paroxysmal stage.

3. The deposition of urates and the ether reaction in the urine indicate an alteration in its colloid state, comparable probably to the colloidal change that is held to occur in the blood during anaphylactic shock.

4. It is probable that the increased ammonia excretion and the retention of chlorides are protective mechanisms.

REFERENCES.

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HAEMOGLOBINURIA AND URTICARIA ARISING FROM COLD.

A NOTE ON THE PRESENCE OF A DERMOLYSIN.*

BY

KENNETH E. HARRIS,† THOMAS LEWIS,
AND JANET M. VAUGHAN.

(From University College Hospital Medical School.)

OBSERVATIONS upon three patients, the first suffering from paroxysmal haemoglobinuria and urticaria, the second from simple cold urticaria, and the third from uncomplicated paroxysmal haemoglobinuria, are here recorded. The investigations are still incomplete; the present note is therefore a preliminary account only.

CASE I.

H. D. is a slightly anaemic girl, aged 11 years; for about two years she has passed dark urine after exposure to cold, such as going out in winter or washing herself in cold water. Apart from a positive Wassermann reaction, given both by herself and by her mother, there is no evidence of congenital syphilis. When tested by bathing in cold water to demonstrate the haemoglobinuria extensive whealing of the skin developed. On further questioning she has given a history of nettle rash appearing after being out in the cold, on exposed areas of the body, and mainly affecting the hands and the face.

The case is typical of paroxysmal haemoglobinuria occurring in response to exposure to cold. This condition has been proved by Donath and Landsteiner,¹ Eason,² and others to be due to the presence in the patient's blood of a haemolysin, which unites with red

* Work undertaken on behalf of the Medical Research Council.
† Assistant on the Medical Unit.