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.

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HAEMOGLOBINURIA AND URTICARIA ARISING FROM COLD.

A NOTE ON THE PRESENCE OF A DERMOLYSIN.*

BY

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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.

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blood cells only at relatively low temperatures, but requires subsequent warming to body temperature to allow the necessary union with complement and consequent haemolysis. This phenomenon has been demonstrated by repeated experiments on the blood of our patient *in vitro*. The skin reaction to cold in this patient is of the usual form seen in other skin injuries—namely, the triple response; cold of the degree here used produces no such response in normal persons. In previous publications from this laboratory^{3, 4} a great deal of evidence has been brought forward to show that this triple response—namely, local reddening, increased permeability leading to whealing, and a reflex arteriolar flare—is due to the liberation of a histamine-like substance already present in the skin cells. The reaction occurs in this patient as a sequel to cold applications, temperatures of from 0° to 19° C. being effective in producing whealing; at 0° C. cooling for only half a minute is sufficient. The reaction is purely local.

The response of the skin to cooling is due to the presence of a dermolysin in the patient's blood. The skin of other subjects is rendered similarly sensitive to cold by the intradermic injection of this patient's serum.

The conditions under which the dermolysin and the haemolysin act are similar. Thus, cooling followed by warming is essential in both instances, and very prolonged cooling is unfavourable to both reactions.

CASE II.

H. M. is an artist, aged 64 years; he was admitted for cardiac failure with venous congestion and slight oedema, but without sign of valvular lesion. There is no history of paroxysmal haemoglobinuria nor evidence of syphilis. Whilst in hospital his skin was found to be abnormally sensitive to cold, and he then gave a history, extending over a period of twenty-five years, of nettlerash occurring on any surface exposed to cold.

In this patient cold produces urticaria locally in the skin; exposure at 0° and 10° C. for ten minutes gives a typical urticarial reaction; but his responses to varying degrees of cold and length of exposure are somewhat variable from day to day. Prolonged exposure of the arms to cold water gives no haemoglobinuria; *in vitro* tests provide no evidence of a haemolysin in his blood. His serum, however, contains a dermolysin, which can be transferred readily to the skins of normal subjects by injection, causing them to react similarly to cold.

CASE III.

W. W. M., a boy of 9 years, had frequent attacks of red urine for three winters, but is said to have had none for the last four years. The attacks always followed exposure to cold. The boy's Wassermann reaction was positive four years ago, but is now negative (he has been receiving antisyphilitic treatment). There is no history of skin eruptions.

This boy, giving as he does a typical history of paroxysmal haemoglobinuria, has at present a haemolysin in the blood, as shown by *in vitro* tests. The skin has been tested with varying degrees of cold from 0° to 15° C., but no whealing can be obtained. The skin of a control subject injected with the patient's serum fails to react to cold.

On the basis of observations upon these three patients, and upon other observations to be described at a later date, we conclude that there are three types of case in which there is a specific reaction to cold—namely, simple haemoglobinuria, simple urticaria, and haemoglobinuria and urticaria combined. The haemoglobinuria in the first and third types is due to a haemolysin, the urticaria of the second and third types to a dermolysin. We have as yet insufficient evidence to show that these two substances are either identical or different, but this question is being investigated further; we have evidence, in their frequent association and in the general resemblance of the corresponding reactions, that the two substances are closely allied pathogenetically.

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RADIUM TREATMENT OF INTRINSIC CARCINOMA OF THE LARYNX.*

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At St. Bartholomew's Hospital researches in radium therapy have been carried out since 1913, and many different types of growth have been treated. At first we employed large doses of radium, either as external applications or buried in the centre of the growths. With these methods it was found that there was too much local destruction of tissues. Radium burns were often produced and the wounds healed slowly. Necrosis and sloughing of deeper tissues were caused, and in many instances secondary haemorrhages occurred. After fifteen years' experience we have come to the conclusion that radium should be buried in the tissues whenever possible, and that as a rule small amounts should be used for long periods. To obtain a uniform irradiation platinum-iridium needles containing radium are buried around the growth, the greatest care being taken to prevent sepsis.

With smaller doses and better technique our results have gradually improved, and four years ago we devised an operation closely resembling that of Professor Bayet for the treatment of intrinsic cancer of the larynx which we hoped might give better results than the more mutilating treatments such as laryngo-fissure and laryngectomy. We have now treated 15 cases of carcinoma of the larynx by this method; in 13 the diagnosis was confirmed by microscopical sections before they were treated.

Method Employed.

A skin incision is made over the thyroid cartilage, starting at the centre of the hyoid bone and extending outwards and downwards along the posterior border of the thyroid cartilage. The infra-hyoid muscles are exposed and split longitudinally. The lateral aspect of the thyroid cartilage is exposed; the perichondrium covering it is divided and stripped backwards and forwards. The greater part of the cartilage is then resected. Thus a large window is made in the thyroid cartilage, but a framework is left consisting of the four margins. By this means the outer surface of the growth covered by the perichondrium is exposed. It is important not to destroy this capsule or to cut into the growth. The cartilage is removed for two reasons—to allow the needles to be placed as close to the growth as possible, and to prevent the perichondritis or necrosis which may be caused by the radium.

From five to ten radium needles are thus inserted lying parallel to one another and vertical. To keep them in position the ends of the needles are tucked under the framework of the cartilage. Care is taken that the needles do not penetrate into the growth or into the larynx. At the lower end of the wound, if the growth is subglottic, the needles are pushed inside the cricoid ring, but in this situation the tissues are often so thin that occasionally the needles may perforate the air passage.

Each needle has attached to it a piece of linen thread soaked in a solution of flavine 1 in 1,000. This material seems to cause less irritation than silk or others that have been tried. The threads are all tied together and buried beneath the muscles. Double sutures are inserted into the skin, half of them being tied at once to close the wound completely, and the other half left so that they can be tied later after the radium has been removed. No drainage is employed, and the skin incision is completely sealed with a collodion dressing. If the growth has extended across the middle line, a second window is made in the thyroid cartilage on the opposite

* A paper read at the Second International Congress of Radiology held at Stockholm.