SOME OBSERVATIONS ON

THE PHYSIOLOGICAL AND PATHOLOGICAL

ACTIONS OF HISTAMINE.

JANUARY 1931.

John Stirling, M.A., M.B., Ch.B.

Shelfield,

Walsall.

Staffs.

Contents.

SOME OBSERVATIONS
ON THE PHYSIOLOGICAL AND PATHOLOGICAL ACTIONS OF HISTAMINE.

This thesis contains a record of work which began with an investigation of asthma and other allergic conditions. Protein sensitisation tests were carried out in a number of asthmatic and other allergic patients with the object of finding out if possible the particular protein to which the patient was susceptible. This led on to a study of histamine and a large number of cases were observed in which the action of histamine explained the mechanism of previously obscure conditions. The skin reaction described by Sir T. Lewis and named the "triple response" was sought for in most cases, and where well marked, was taken to indicate that such persons had a rich supply of histamine or other similar substance, ready to be released into the system under certain stimulation.

Histamine is derived from the amino acid, histidin, by removal of CO_2. G. Hunter (Biochemical Journal 1922) isolated histidin from the urine from a case of measles, and described a modification of Knoop's test for histidin. This test has been suggested for the diagnosis of early pregnancy. In the examination of cases other than pregnancies, it was noted that a considerable number gave a positive result. This test, therefore, was carried out in a number of cases of the skin conditions, and all other conditions where one had reason to believe that there might be excessive liberation of histamine.

By combining the skin sensitisation tests, the stroke reaction giving the "triple response" and Hunter's modification of Knoop' test, an attempt was made to find out if in cases of "histamine shock", some allied substance was excreted in the urine.

As it has been suggested that deficient blood calcium leads to increased permeability of capillary walls, a number of estimations of blood calcium were made, and are included since they help to substantiate certain of the deductions.

It is a common observation that a certain proportion of individuals are very susceptible to substances which are perfectly harmless to other people. A susceptible person, on exposure to a minute dose of a commonly accepted inert substance may manifest very severe symptoms in a very short time. These symptoms may be purely local, but if the sensitiveness is very intimate, severe systemic disturbances may take place, which may have a rapidly fatal termination. At different times this condition has been referred to as idiosyncrasy, hypersensitiveness, anaphylaxis, allergy and "histamine shock"

During the past few years, asthma and kindred conditions have been the subject of a great deal of research. The ingenious hay-fever theory of Blackley, was not commonly accepted till a quarter of a century later, when the experimental work of Behring and Richet on anaphylaxis in 1902, gave it a scientific basis. In 1903, Langois and Wolff Eisner independently pointed out the anaphylactic nature of hay-fever. Gradually there has emerged from this work the conception of a group of diseases which Freeman has termed "the toxic idiopathies due to a sensitisation to particular proteins"

This group of diseases includes asthma, hay-fever, angioneurotic oedema, certain forms of eczema, urticaria, and certain types of gastro-intestinal disturbances. Some authorities go further and include prurigo, dermatitis herpetiformis, migraine, cyclical vomiting and certain forms of epilepsy.

Probably at the present time, no disease group shows such a varied and complex causation, but many of the obscurities have been recently explained by researches in anaphylaxis and idiosyncrasy. The important part played by extraneous proteins in the genesis of asthma and the obvious analogy between the asthmatic attack and the symptoms of anaphylactic shock, have suggested that in many cases, if not all, asthma is an anaphylactic phenomenon.

In anaphylactic shock the symptom complex is due to the presence of foreign proteins in the blood, and in this thesis the suggestion is put forward that asthma and

other allergic conditions are due to toxic proteins derived from some fault in the protein metabolism of the body.

The researches of Sir T. Lewis on the blood vessels of the skin, and the action of the substance which he called the "H" substance responsible for the phenomena of the "triple response", and the work of Dr. Dale on histamine, have thrown new light on the problem of allergic disease.

The action of histamine will be demonstrated in a large variety of diseases: asthma, acute pulmonary oedema, urticaria, angio-neurotic oedema, measles, scarlet fever, the bronchial and intestinal disturbances associated with eruption of teeth in babies, allergic epilepsy, purpura haemorrhagica, and various conditions of hypersensitivity.

All the cases reported were, with one exception, met with during the ordinary routine of general practice in an industrial area.

Histamine is one of the most powerful depressor and oxytocic substances known. The oxytocic power is such that a concentration of one in 250 million parts will stimulate guinea pig uterus.

It was first made synthetically as a chemical curiosity by Windaus and Vogt.

Barger and Dale in 1910 isolated an active principle from ergot which produced symptoms resembling asthma, and which was found to be histamine.

The first definite claim to the chemical identification of histamine as the essential depressor constituent of a number of animal organs was made by Abel and Kubota in 1919.

About 1928, liver extracts were used for the treatment of morbidly high blood pressure, and when the chemical substances responsible for the depressor action were investigated, choline, and histamine were isolated from the liver extract. Attention was next turned to the lung which yielded an extract having a very intense depressor action, and histamine was isolated with little difficulty.

THE BIOCHEMISTRY OF THE AMINO-ACIDS.

Proteins may be regarded as the most important of the three classes of foodstuffs, proteins, fats and carbo hydrates.

When proteins are heated in a reflex condenser with dilute mineral acid, a series of hydrolyses takes place resulting in a gradual breaking down of the large protein molecules into smaller ones. At first proteoses are formed, then peptones, and later a mixture of amino acids. The amino acids can be separated by various complex procedures, and so far twenty have been obtained and definitely identified. They are essentially both substitutes ammonias R.NH_2 and carboxyl acids, and most have the type formula $R - \overset{NH_2}{\underset{H}{C}} - COOH$.

In virtue of this double property of being at the same time base and acid, the amino acids are all amphoteric, reacting as bases with acids, and as acids with bases. They are "amphoteric electrolytes" or "ampholytes" and ionise very slightly in solution in two ways.

Glycin, $NH_2\ CH_2\ COOH$, the simplest, typifies the behaviour of all

(1) $NH_2\ CH_2\ COOH \rightarrow NH_2\ CH_2\ COO^- + H^+$.

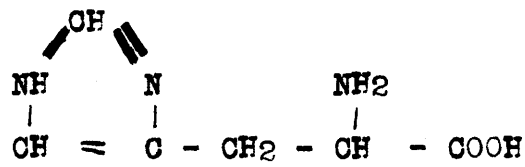
(2) $COOH\ CH_2\ NH_2 + HOH \rightarrow COOH\ CH_2\ NH_3\ OH \rightarrow COOH\ CH_2\ NH_3^+ + OH^-$.

The second series of changes parallel the formation of ammonium ions.

$NH_3 + HOH \rightarrow NH_4\ OH \rightarrow NH_4^+ + OH^-$.

The extent to which these two types of ionisation takes place depends on the pH of the solution. If alkaline, the first is the main change, and from such, alkaline salts of amino-acids will crystallise. If acid, the second takes place and acid salts will crystallise.

For our purpose, an important amino acid is Histidin, - b - iminazolyl - a - amino - proprionic acid which has the formula

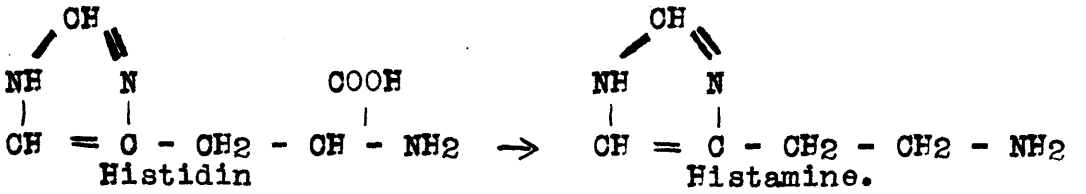


Histidin is present in most ordinary foods.

During digestion, food is acted on by different enzymes. In the stomach, the gastric secretion may be regarded as a 0. 4% solution of Hydrochloric acid, containing the enzymes pepsin and rennet and traces of gastric lipase. Pepsin is a powerful protease, and digests proteins in an acid medium. The action of pepsin on proteins is very similar to that of hot dilute acid, a series of hydrolyses resulting. The action is more limited however, seeming not to pass the peptone stage. Passing out of the stomach the food is acted on by the intestinal juices and bile. The most powerful enzyme acting on the broken down proteins is trypsin which carries the hydrolyses to the polypeptide and amino-acid stage. The intestinal enzyme, erepsin, splits up the peptide linkage. It acts forcefully on proteoses and peptones, rapidly setting free the constituent amino-acids.

In the intestine where bacteria abound, the - - - amino-acids are again broken down into different compounds, some of which have a high degree of toxicity. The actions of bacteria on amino-acids are of two kinds, they may either at first deaminise the acid, producing ammonia and a derived fatty acid and then subsequently split off CO_2 from this, leaving derived phenols, or else they may split of CO_2 at once, producing a more toxic amine. Deaminization takes place in alkaline medum, and decarboxylation in acid medium. e.g. - Tyrosin in alkaline medum is deaminized to para-cresol and phenol, and in acid medium is decarboxylated to tyramime. Tryptophane in alkaline medium → Skatole and indole and in acid medium → Tryptamine.

Decarboxylation of histidin in acid medium → histamine



In a buffered or alkaline medium histidin is either not catabolised or it is catabolised with the production of substances which do not contain this imidazole ring (Hanke and Koessler, Jour. Biolog. Chem. 1924)

The amines, acids, and phenols formed by bacterial action are all absorbable through the intestinal wall, and some are usually present in the urine. The ease with which they can be absorbed suggests that they may be responsible for certain symptoms of toxicity in the organism.

Many of the amines from ethylamine, (which produces

slight effects) up to tyramine, when injected into the blood stream produce a marked rise in blood pressure acting as constrictors of the smooth muscle of the arterioles. This effect is produced to a still greater extent by adrenin (a product of the adrenal glands and a derivative of tyramine) Their action is similar to stimulation of the sympathetic nervous system, and so they have been called sympathomimetic.

Histamine on the other hand, when injected into a vein causes immediate fall in blood pressure with rise of body temperature and bronchial spasm. It is a powerful stimulator of smooth muscle.

As most of the ordinary foods contain histidin, and as normally the intestinal tract is rich in bacteria, a supply of histamine is normally found in the intestine.

TABLE SHOWING AMOUNTS OF HISTIDIN IN VARIOUS FOOD ETC. (BIOCHEMISTRY OF AMINO ACIDS- MITCHELL AND HAMILTON)

PROTEIN.	CHARACTER OF PROTEIN.	NITROGEN CONTENT.	% OF TOTAL NITROGEN IN FORM OF HISTIDIN
Milk	Casein	15·62	6·2
	Lactalbumin	15·49	4·6
Blood	Fibrin	16·91	4·8 - 3·4
Muscle (ox)	Coagulable Protein	16·67	5.9
Hen	Myosin from Muscle	16·47	3·3
	Myogen from Muscle	15·01	6·6
Egg	Yolk	-	3·1
	White (Egg albumin)	15·51	4·0 - 0·2
Corn	-	-	4·8
Oats	-	-	5·8
Dog	Hair	-	3·5
Cabbage leaf	Soluble in alkali	-	11·5
Cauliflower	Water soluble	-	2.7
	Alkali soluble	-	6·1
Carrot	Water soluble	14·72	4.4
Parsnip	Water soluble	12·12	11·5

Histamine is also present in body tissue. Thorpe (Biochem. Journal 1928) gives the following amounts in mgrms. per kilo.

Lungs	35 - 75.	Bladder	7 - 8.	Muscle	1 - 1.4.
Skin	24.	Spleen	5 - 7.	Kidney	2 - 3.
Ovary	9.	Liver	2 - 6.	Thyroid	0.5.

It will be noted that the lungs and skin have a high histamine content.

Since amines are derived from amino-acids only in acid medium, and this protective mechanism is resorted to when the accumulation of H-ions is incompatible with normal life processes, so amines may be regarded as "reaction buffers"

It has been shown that some of the amines functionate best at a pH similar to that of pulmonary arterial blood when the CO2 tension is lowest. This probably explains the selective action of histamine for the pulmonary area. The pH of the blood in normal person lies between 7.30 and 7.45

In Clinical Interpretation of Aids to Diagnosis Vol. 1,p. 328-9., it is shown that interference with respiration due to disease of heart or lungs, gives a disturbance of the acid-base balance and the pH may fall to 7.10.

THE ACTION OF HISTAMINE.

Drs. Dale and Laidlaw, (Medical Research Committee Report No. 28), show that histamine has an intense stimulatory effect on plain muscle including that of arteries.

Injection of 1-2 mgrm. per kilo. body weight into cats leads to respiratory distress due to constriction of the bronchial muscles, and rise in blood pressure due to contraction of the muscles of the arterioles. Very soon, a sudden fall in blood pressure takes place, becoming profound in 4-5 minutes. The heart acts vigorously and its failure is not the cause of the fall in blood pressure. Nor is arterial dilatation the cause as the vessels appear constricted. The blood is found in the smallest blood vessels which are dilated. There is concentration of red blood corpuscles, loss of blood plasma, and oedema of the tissues of the skin. The lungs become full of bubbling rales, and increased secretion in the trachea often is blood stained.

In the dog and monkey, the arterioles are relaxed, and in man, the relaxation appears to spread further up the arterial tree from the capillaries. Otherwise, the condition in the cat, dog monkey and man is the same.

This sequence of capillary dilatation, an opening up of channels which under normal conditions have only a potential existence, an abnormal permeability of the capillary walls leading to transudation of plasma, and

finally a stagnation of the blood in these widened channels, is familiar as signs of mild inflammation.

The writer who gets mild asthmatic attacks only on exposure to fumes of brickworks, or products of incomplete combustion of coal, or badly ventilated gas fire, had an injection of ergamin. acidi phos. which contained 1 mgm. of histamine, with the following results:-

Previous to the injection the blood pressure was $\frac{132}{90}$, P.R. 76. The urine was examined by the Hunter modification of Knoop's bromine water test and was negative. Within two minutes a sensation of heat was felt over the face and hands. They looked red. The cutaneous dilatation was not so marked on the trunk. At the site of the injection in the middle of the forearm, a large irregular wheal developed 1¼" in diameter with a flare extending over most of the forearm. In about four minutes slight difficulty of respiration - expiratory distress was noticed. This gradually got worse until a well developed mild asthmatic attack was established. The face was very flushed; the colour being bright red, and it felt hot to the touch. There was also marked throbbing in the temples with dull aching pain. No alteration of temperature taken under the tongue was noted. The blood pressure was noted at intervals. In about twenty minutes, coughing brought up a small plug of mucus and the attack rapidly passed off. Restoration to normal took place in about 35 minutes. There was also a desire to empty the bladder.

	Before	2 min. after	4 min.	8 min.	12 min.	20 min.
Blood Pressure Systolic (Tycos)	132	110	95	105	126	128
Diastolic	90	76	70	78	86	86
Pulse rate	76	120	132	100	86	80

A specimen of urine taken at the end of half an hour from the injection gave a strongly positive bromine water reaction.

If histamine is applied to scarified skin, within a few minutes a large spreading area of marked redness appears, radiating from the scratch. This is due to dilatation of the capillaries. The skin round the scratch soon begins to swell and become pale, and a large wheal, pseudopodic in outline develops, having the scratch near its centre.

Bacterial poisons which cause intense inflammatory reaction will produce a profound shock-like collapse of the circulation if rapidly distributed through the system. Products liberated from injured tissues also cause shock-like failure of circulation. In these reactions there is marked similarity.

There is also evidence to support the view that not only mechanical injury, but lack of oxygen, due to deficient blood supply, will initiate changes which lead to appearance of substances having this type of action. If the blood supply be cut off from hind legs of a cat, the readmission is followed by dilatation of cutaneous vessels in these, and also in forelegs, which have been rendered sensitive, by denervation, to the action of histamine and other substances.

Bayliss and Cannon in the same Medical

Research Report show that there is a slow formation of fixed acids in tissues deprived of circulation. These have similar dilating effect on capillaries when circulation is restarted. The defective circulation tends to further formation of substances dilating capillaries and so the defect is maintained and accentuated in a kind of vicious circle..

Histamine, therefore, is a very powerful substance which is present in the lower intestine, and if absorption took place readily, serious results might follow. There appears to be some defensive mechanism which the organism possesses against an excessive absorption. Adrenalin has an opposite effect to histamine.

The organ which ordinarily is presumed to bear the main burden of detoxication of intestinal poisons is the liver, but no actual destruction of histamine has been demonstrated.

Drs. Dale and Laidlaw perfused surviving liver with histamine, but no evidence of imidazole acetic acid was obtained though a certain proportion of histamine disappeared.

Another suggestion put forth by Koessler and Hanke is that "Histamine may be rendered pharmacologically inert in its passage through the wall of the intestine, which renders innocuous a highly toxic intestinal bacterial product"

In this case, histamine only is absorbed if there is some damage to the intestinal mucosa. Disease

of the intestine or stasis may allow absorption and so explain the mechanism of a number of disorders on a histamine basis.

The onset of typhoid or paratyphoid fever is often characterised by headache, increased respiratory rate, signs of mild bronchitis, abdominal uneasiness and fall in blood pressure. The chest symptoms may lead to an initial diagnosis of pneumonia. This may in part be due to excessive liberation of histamine through the damaged wall of the bowel. The bromine water test gives a definitely positive result during the active stage of the disease, and becomes negative when recovery is taking place.

Dr. Dale suggests that the large amount of histamine found in the lung, might represent material which having served its purpose in other parts of the body, was carried for destruction to the lungs. The suggestion that histamine is a true lung hormone is purely theoretical.

ANAPHYLAXIS.

If an animal be injected subcutaneously or intravenously with any foreign protein - like substance whether toxic or not, a subsequent injection of a small amount of the same, and only the same material, produces a very rapid, severe and often fatal poisoning which is always of the same type, no matter what foreign protein is given. The symptom complex may be different in different species. In dogs, it is shown by vomiting, purgation, respiratory distress, and general muscular weakness, later leading to insensibility.

In guinea pigs, spasm of the bronchial muscles is the characteristic feature.

Similar symptoms are produced by injection of Witte's peptone which contains histamine. Consequently it was assumed that anaphylactic poison was identical with substance in this peptone. It appeared that owing to the first injection of the antigen (foreign protein), a specific antibody had been gradually formed in the body which, when it met the same antigen, produced a body which could liberate the anaphylactic poison and so produce the shock. This assumption, of a poison-anaphylatoxin-circulating in the blood is no longer tenable.

Dr. Dale - (Journal Pharmacology 1913 Vol. 4) shows that smooth muscle - gut, uterus, or bronchi- from a guinea pig previously treated with an antigen and washed completely free of blood and serum, is extremely

and specifically sensitive to a single administration of even minute traces of the antigen used.

This suggests that the first injection of antigen, after a definite incubation period, produces a complamentary substance which makes the cell ready to fix on any trace of antigen, and so liberates histamine.

This conception of anaphylaxis as specific cellular sensitivity brings it close to the analogous remarkable symptoms of tissue hypersensitivity after injections of vaccines, hay fever poisons, poisons by certain plants and also certain idiosyncrasies noted with definite chemical substances e.g. iodine, etc, all of which in predisposed individuals regularly produce exanthemata, or oedema, or other signs of shock.

In confirmation of this view, the analogy or relationship of anaphylaxis and idiosyncrasy is supported by the following considerations-

(1) Both in anaphylactic shock and idiosyncrasy attacks, the symptom complex is typical, and in the same individual or animal species is always the same, quite independent of the chemical character of the antigen, or of the poison, consisting, in each case, either of bronchial spasm or skin oedema, and exanthemata depending on the species and the predisposition.

(2) Symptoms of anaphylaxis and of idiosyncrasy are always produced by a substance specific for each case and of definite chemical type, the first by

antigen used, the other in a hypersensitive individual by the particular poison to which he is sensitive whether it be food, inhaled pollen, or animal poison, or contact with irritant e.g. iodine, or particular plant.

(3) Before and during commencement of a sensitisation it is possible, by cautious treatment, with antigen or poison, to weaken the reaction so that it is not apparent, and so produce a satisfaction of the specific cells and therefore for a time, lack of sensitivity, anti-anaphylaxis or disappearance of idiosyncrasy.

(4) One point of difference - anaphylaxis can be produced in every mammal but idiosyncrasy depends on inherited or acquired predisposition.

The analogy between anaphylaxis and histamine shock has already been referred to.

Histamine shock varies in different people when produced by injection of histamine subcutaneously. In some individuals the usual characteristics of cutaneous flushes, increase in respiratory rate, fall in blood pressure are the only manifestations. In certain individuals who are subject to asthmatic attacks, injection produces a typical attack. In cardiac cases it leads to onset of cardiac asthma.

INFLUENCE OF HISTAMINE ON GASTRIC SECRETION OF INFANTS AND CHILDREN - (DR. A.V. NEALE - ARCHIVES OF DISEASE IN CHILDHOOD 1930 - VOL XXV137)

In 1922 Carnot observed an active secretion of acid gastric juice in adults following the injection of histamine. The dose sufficient to produce maximal flow of gastric juice, produces only a transitory effect on the circulation - flushing of the skin.

The general character of the curve of secretion volume is similar in all persons, there being a rapid rise in volume during 30 minutes immediately following injection of histamine and a continued fall for 60 minutes when the previous resting stage is regained. Active secretion of peptic enzyme also follows injection of histamine.

There appears little doubt that gastric secretion following histamine injection is physiological in nature and represents the maximal functional level of the gastric secretory power in the individual concerned.

Histamine injection in pernicious anaemia fails to produce any acid gastric secretion. By this means true achylia gastricia is confirmed.

In Dr. Neale's experiments with children, histamine (Roche) was used in the following doses:-

½ - 1½ years..... 0·15 mgrm.

4 - 6 years..... 0·2 mgrm.

10 - 12 years..... 0·3 mgrm.

In the case of infants, histamine was injected subcutaneously after an interval of 4 - 5 hours from the last feed which should be glucose water instead of milk.

In the other children, the experiment was carried out after a night's fast.

Any gastric contents are removed before the injection.

Every fifteen minutes for one hour the stomach contents are removed by suction.

From the data obtained the chloride - secreting power of the stomach, and the volumetric response to a fixed adequate stimulus is determined.

Chart 1. shows the secretion of acid in the gastric juice of normal healthy children in three distinct age groups. The acidity reaches its maximum within 30 minutes, and falls always within an hour. In each age group there is considerable range of maximal activity, but the type of curve is the same.

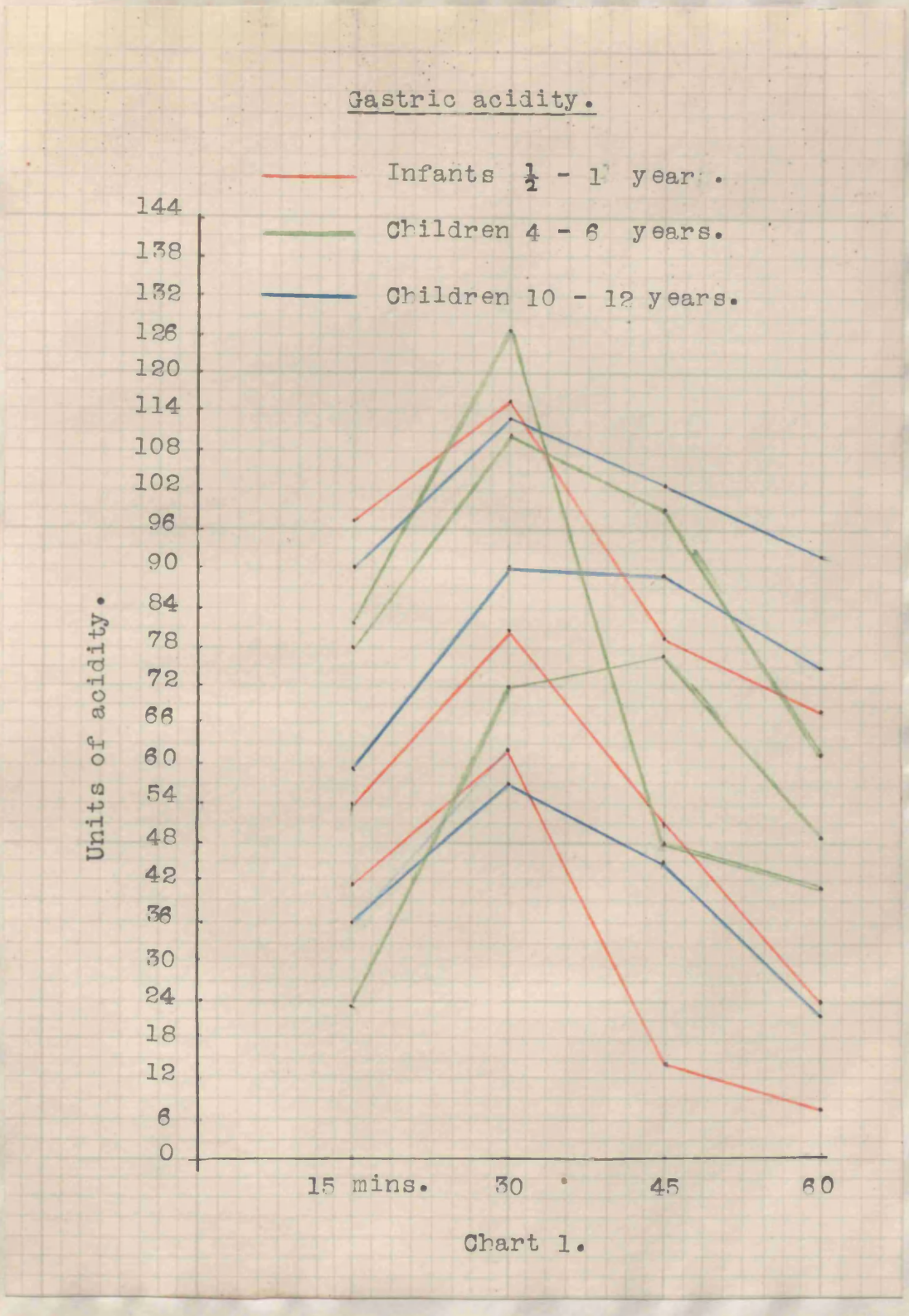

Gastric acidity.
Infants ½ - 1 year.
Children 4 - 6 years.
Children 10 - 12 years.
144
138
132
126
120
114
108
102
96
90
84
78
72
66
60
54
48
42
36
30
24
18
12
6
0
Units of acidity.
15 mins.
30
45
60

Chart 1.

Chart 2 shows the volume of gastric juice following the fixed adequate dose of histamine. Injections of histamine leads to increased secretion of gastric hydrochloric acid. This fact probably explains why gastric ulcer is sometimes associated with severe burns. A large supply of histamine is liberated in the body, and as gastric ulcer is practically never found except when the acid content is high, the extra stimulation by histamine, and secretion in the stomach may predispose to the ulcer formation. A person who has been severely scalded or burned is also very liable to bronchial complications.

The volume of gastric juice is very low in children in first year, which suggests that gastric secretion in infants does not play an important part in normal digestion, as in older children. More copious secretion is possibly a provision for the digestion of the more solid food stuffs.

Volume of gastric juice in the three age groups.

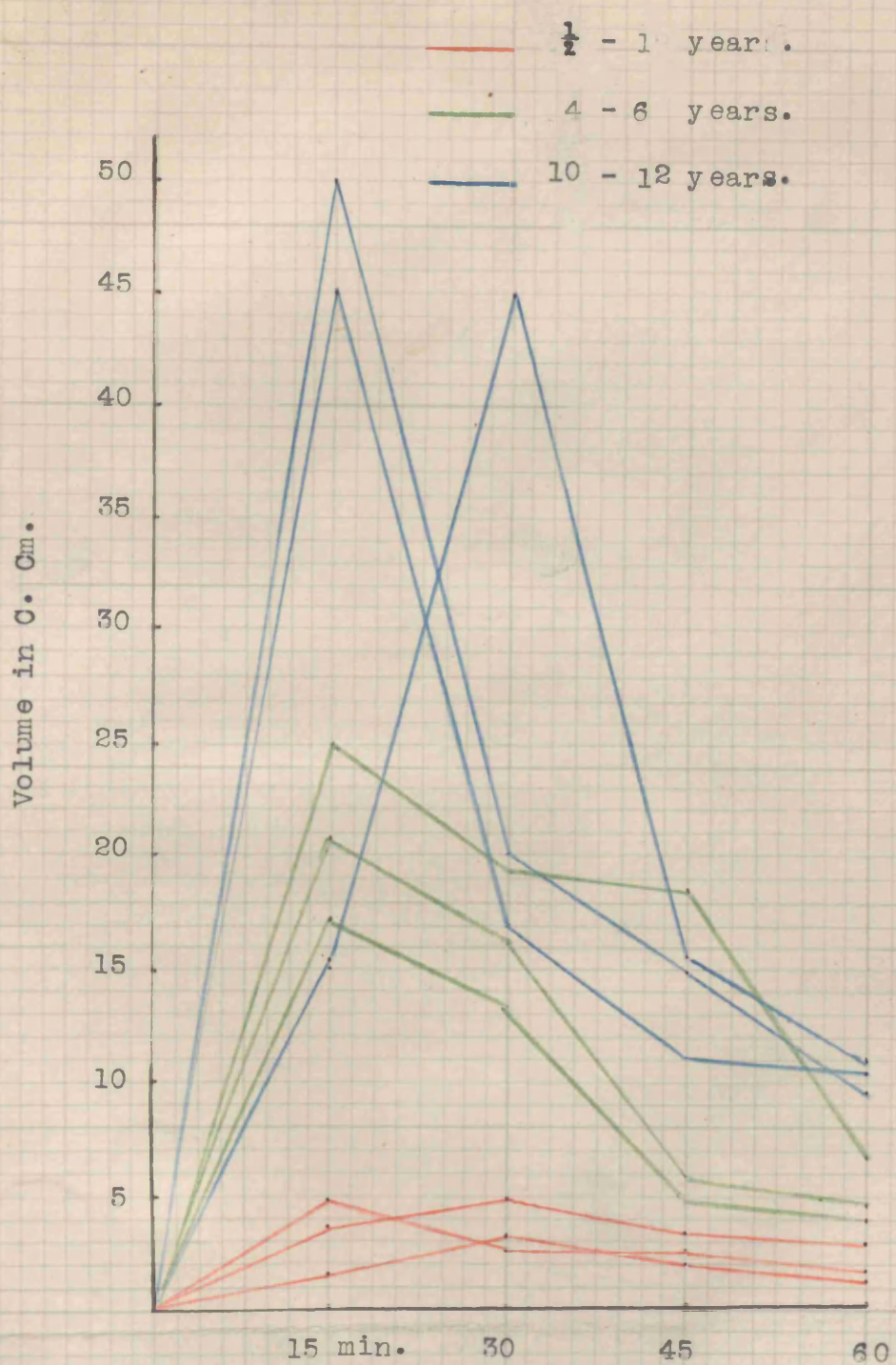


Chart 2.

THE ACTION OF HISTAMINE ON THE BLADDER.

Histamine is a very powerful stimulant of unstriped muscles, and experiment shows that when histamine is injected subcutaneously, one of the actions is to stimulate the bladder muscles.

In several cases, soon after an injection of histamine, the patient expressed the desire to empty the bladder, and in others though the condition was not urgent, the desire was present.

After a hot bath, when histamine is liberated in large quantity, it is very noticable that stimulation of the bladder takes place even although the organ has been emptied a very short time before.

After a cold bath, when one gets a good skin reaction following towel friction, histamine is liberated, and the bladder action is the rule.

In cases of asthma, during the acute attack, incontinence of the bladder is a common complaint.

In two of the recorded cases of acute pulmonary oedema, incontinence was a feature, and this was also noted by Dr. Bradford in the case of cardiac disease which was given an injection of histamine.

Investigation of this action was carried out in a number of cases of measles. In adults, interrogation elicited the fact that there was marked frequency of micturition during the acute stage of the disease, and that this passed off gradually with the

fading of the rash.

In the case of children, the mothers stated that children who had previously been clean in their habits were different during the acute stage, the bowels and bladder often acting involuntarily. In some cases the habit persisted for a considerable time after the child had recovered.

In a recent case of severe scalding, a little boy aged 3, who had been clean in his habits, changed completely. During the whole period of the acute stage of his illness, the bladder emptied itself every time the child fell asleep, and now, nine months after recovery, nocturnal incontinence is very frequent.

The emptying of the bladder usually depends on a reflex controlled by will. The impulse causes contraction of the fundus, and relaxation of the sphincter. The reflex closure of the bladder, which is produced by the voluntary contraction of the perineal musculature, causes the fundus to relax and the sphincter to close by impulse passing through the sympathetic fibres of the hypogastric plexus. Adrenalin and ephedrine contract the trigone and relax the fundus. Occasionally one finds that the injection of adrenalin for the relief of an asthmatic attack leads to retention of urine.

The use of ephedrine or adrenalin in the treatment of nocturnal incontinence of children appears to be justified. Dr. Parkhurst (B.M.J. Dec. 27. 1930) regards these drugs as almost "specifics" after personal experience of over 5 years of their use.

The researches of Sir Thomas Lewis have an important bearing on this subject. He showed that when the living cells of the skin were subjected to irritation or injury they liberated a substance very like histamine. Chemically identical histamine has not been obtained from the skin, but a substance physiologically identical has been extracted. Dr. Dale makes the suggestion that if the "H" substance of Lewis was not histamine, it was a substance immediately yeilding histamine. The "triple response" of Lewis is as follows:-

If the skin is stroked with a pencil, say, within a few seconds, a red mark shows along the line of stroke; this is called the "red tache", and is caused by dilatation of the minute skin vessels, arterioles, capillaries and venules. On both sides of the tache, radiating away from the stimulated area, a bright scarlet flare appears in about 10-30 seconds; this is called the "flare" or reflex erythema and is due to dilatation of the arched arterioles of the skin. It disappears more quickly than the tache.

Along the line of stroke, in certain cases, a wheal develops, due to diffusion of fluid through the capillary walls, whose permeability have been increased. This appears in a few minutes. This triple response - Tache, flare and wheal - may be elicited by mechanical, thermal, and chemical stimulation and the common causal factor was named the "H" substance by Lewis, and, as indicated, is probably histamine. This reaction was tested in a great many of the cases under review.

In well marked cases of whealing, the end result was exactly similar in appearance to the wheal produced by histamine scarification of the skin and also to the reaction to the offending protein in a sensitive individual.

The number of strokes necessary to produce a wheal is a measure of the rate at which the cells liberate histamine.

In a susceptible individual one stroke may be sufficient to give a very marked reaction, while in another ten strokes may produce only a very slight response.

STROKE REACTION.

As a general rule - infants show good reaction.

Those children which wheal very rapidly are more susceptible to bronchial and intestinal disturbances of teething.

The stroke responses are marked in cardiac cases, asthmatics and other allergic conditions.

Individuals who are hypersensitive to various substances, e.g. iodine, plants, gnat toxines, usually show brisk responses.

Histamine scratch inoculation during the eruptive stage of measles develops more rapidly than when laid down during the fading stage.

Increased calcium in the blood delays

the stroke reaction - more strokes are required to produce a wheal after calcium adminstration than before it.

Whenever the skin displays an acute reaction in the form of the "triple response" the reaction is due to histamine. Histamine is liberated in response to injuries.

There is a striking resemblance between wound shock and histamine shock. When tissues are severely injured certain substances are released into the circulation which in their action resemble histamine. If a tourniquet is applied to an injured limb immediately following the injury, the released substances do not get into the circulation so rapidly, and the onset of shock is delayed. Liberation of histamine in small quantities in the skin will lead only to the local response, but if through extensive and severe mechanical injury of the skin, greater quantities are liberated, these may lead to the general action, bronchospasm, dilatation of capillaries with transudates, fall in blood pressure - in fact a condition of secondary shock.

The action of heat on the skin gives a typical example.

In a mild degree, the local action only is present. Normal skin shows a certain mottling, and this mottling becomes more marked if an area is exposed to heat. The darker areas of skin are relatively unresistant, and the vessels in these areas undergo exaggerated expansion. The skin pigments more deeply on these areas. This is well demonstrated in the pigmentation frequently seen on legs which have been scorched at a fire.

Careful observation of a case of measles shows that the rash appears in dark mottled areas. This mottling is also clearly seen in the fading flare following the ordinary stroke reaction.

Prolonged action of heat on a limited area leads to marked increased permeability and the blister is formed.

More extensive burning gives a very large liberation of histamine, and the general action is more pronounced leading to a condition of shock.

From the simple responses of healthy skin to stimuli through more severe though still trivial local injuries, e.g. burns and blisters, to the more serious effects of mechanical injuries and severe burning, we pass by simple transition. The reaction is one of quantity not quality.

COLD.

If snow is handled, a red colour develops similar to heat, though a slight initial cyanosis precedes the redness.

As the skin temperature falls, the rate of blood flow falls, and also the rate of oxygen exchange, so that with cold the oxygenation of the skin is deficient and redness results.

The oxygen saturation of the venous blood approaches that of the arteries because at low temperatures the tissues are unable to utilise the available oxygen.

If the skin is sprayed with ethyl chloride, the first effect is local redness if the freezing is kept up for a short period. Longer exposure gives a flare, and still longer gives a wheale. Destruction of the tissues similar to burning is produced by CO2 snow. The wheal is in this case produced by loss of tone of the vessels, which renders the wall more permeable.

When a cold hand is heated, the reddening is not produced by the action of heat, but by the liberation of histamine, deficient oxygenation leading to liberation of vaso-dilator substance.

Cold lessens tone of vessels. Redness with cold is due to loss of tone. Redness after heating cold arm is due to histamine indirectly liberated owing to deficient oxygenation or tissue damage.

Cold in the first instance causes a contraction of the small blood vessels of the skin and when stimulus is removed a reactionary vaso-dilatation takes place. This is due to the liberation of histamine and the increased permeability of the capillary walls leads to localised oedema.

Erythema pernio - chilblains - is frequently seen in young and old poeple - usually in those where the peripheral circulation is poor.

Acrocyanosis is a condition frequently met with in young women, characterised by persistent blueness of the extremities - hands and feet - nose and ears. Since the introduction of the short skirt, the lower half of the legs is the part chiefly affected. The skin is cold to

the touch. This is probably due to the contraction of the arteries to the part. Such patients are very liable to chilblains. Calcium deficiency has been suggested as the cause, also deficiency of endocrine secretion.

Four cases of this condition (No's 9, 10, 11 and 12) were examined for calcium content of serum, and the figures were all slightly below the normal:- 9·6, 8·8, 10·0 and 9·4. The mechanism of chilblains formation in such cases may be explained as follows:- Initial contraction of arteries supplying the part - leading to cyanosis and consequent lack of oxygenation in the tissues (local asphyxia) When the patient enters a warm room the blood supply is restored. Histamine is liberated, causing dilatation of the capillaries, and increased permeability of the walls with exudation of lymph into the tissues in localised areas where the circulation is worst and in which the liberation of histamine is greatest. These areas can be often clearly seen as bright red areas surrounded, and shown up by, the blue areas.

Some people are more sensitive to stimuli than others. This is specially noted if a large number of cases are examined for the "triple response" Some wheal with but one stroke while others show the faintest flare after a dozen strokes. Increased sensitivity means increased tendency of the cells to release histamine.

There is a marked similarity also between the histamine response and anaphylactic phenomena both in the local and general response.

It is clear that a single fundamental cause must be postulated to explain this. There are two possibilities-

(1) That the anaphylactic poison liberates histamine and the response (local or general) is due to the liberation - Sir T. Lewis.

or (2) That the histamine affects the reacting cells by producing in them a physical change of a kind identical with that produced in them when stimulated in anaphylaxis - Dr's Dale and Laidlaw.

That a common physical change in the reacting cells is an end result in both is clear. In both cases, the cells act similarly - constriction of unstriped muscle, relaxation and increased permeability of capillary walls resulting.

The first view ascribes the action to a single cause. The second view suggests a physical change - the common end result either of their action with histamine or of interaction within them of antigen and antibody.

LIBERATION OF HISTAMINE DUE TO RADIATION WITH ULTRA VIOLET LIGHT.

Just as the action of sunshine on the skin cells liberates histamine, so does artificial light as exhibited by ultraviolet rays - artificial sunlight. The following case is interesting- Mrs. C. aet 34, suffering from lupus vulgaris restricted to the lobes of both ears, received treatment by ultra-violet light. Immediately following exposure she

complained of flushing of the face and hands, giddiness, faintness and a feeling of depression. Within two hours she had rather severe diarrhoea. This sequence of events followed every treatment until it was decided to discontinue on account of the general disturbance. In this case the skin manifestations were marked and were followed by stimulation of the smooth muscle of the intestinal tract.

Her skin reaction as tested for Lewis "triple response" were very marked, the flare being very pronounced and the wheal developing rapidly.

Injections of 1 c.c. Armour's 7½% solution of Peptone led to exactly similar conditions. In this case, the first specimen of urine obtained after the injection gave a positive bromine water test, the specimen obtained before injection being negative.

During the past Summer an unusually large number of patients have been seen suffering from severe skin inflammatory conditions, due to gnat bites. In several cases practically the whole of the skin from the ankles to the knees was acute inflamed, red, hot and tender. Capillary dilatation was noted, and transudation of serum through the capillary walls was demonstrated by pitting of the skin on pressure. Urine from 15 cases gave a positive bromine water test.

In these cases, histamine in large quantities was liberated by the action of the injected gnat toxin, on the cells of the skin..

In dealing with cutaneous eruptions in different diseases and correlating these with the action of histamine, two main types of eruption are recognised by Lewis.

The first type - the morbilliform or macular - shown in local reaction, is two-fold in nature, active dilatation of capillaries with increased permeability.

The second type - the scarlatiniform - shows a widespread flare, due to opening up of strong arterioles and diffuse scarlet blush of irregular outline. It appears mottled as it fades or while it lasts. It is due when provoked by local injury to a local reflex through terminal branches of sensory nerves, and then, like the first type, by the release of histamine.

When the two types occur in combination as they frequently do, in response to powerful artificial stimulation - for both are produced by histamine - they produce a composite eruption - urticaria.

It is concluded that all simple macular eruptions and all those of urticarial type are due irrespective of clinical association to release of histamine in the skin, and that the area covered by the red spots, wheal or simple blister, marks with precision the area of skin in which the histamine has been released and that is released in one of two ways.

(1) Direct injury of cutaneous cells by injury or circulatory or entrapped poisons.

(2) Through antidromic impulses.

The appearance of the symptoms will depend on several factors, namely-

(a) The distribution of the poison.

(b) The potency or rapidity with which the poison injures the cells and liberates the histamine.

(c) The time the poison lies in active form in skin.

(d) Its diffusibility.

(e) The reactivity of vessels and nerve endings to the histamine released.

Urticaria. The rash consists of widespread erythema in centre of which a wheale develops. The condition is due to a very rapid poisoning of cutaneous cells, and histamine is released in large quantities. Rapid outpouring of lymph produces the wheal. After the discharge of the dose of poisoning substance, there is a rapid disappearance of the rash.

Macular Rash. The poison is slower in action than in the case of urticaria. It is more persistent in its action and is due to presence of poison which acts with less protency and longer than in urticaria or to a stimulus which damages cells slightly, but in such a way as to continue to liberate histamine slowly and for a relatively longer period.

The slow development is responsible for

the absence of conspicuous oedema.

The raised macule is due to poison which acts quicker and so gives oedema.

The blister is a further step in the same process, the more rapid action giving greater permeability.

In haemorrhagic eruptions the walls are dilated and particularly permeable. We may deduce that the same poison which produces the macule, raised macule and blister, may tend to damage the walls of minute vessels and cause haemorrhage into the tissues surrounding.

The mechanism is identical, the only difference being the severity of the poison. The following case of purpura haemorrhagica presents some interesting features:-

J.H., Girl, aged 8 months - whooping cough at 5 months, followed by purpuric spots all over the skin of trunk, arms and legs, and mucous membranes of nose and mouth. On testing for the "triple response", a well marked flare developed. Instead of the ordinary whealing, the exudation of lymph appeared first of all in small circular areas, most of which contained in the centre a purpuric spot. Some wheal areas had no spot visible to the naked eye, but examination by a lens showed a rather darker centre. These spots were marked, and subsequent examination revealed a purpuric spot. This curious reaction showed that the liberation of histamine was greater in some areas than others, and that the area where haemorrhage had taken place was the centre of liberation.

Only on two other occasions with cases of urticaria, was this type of reaction noted. In these cases, both of whom had a well marked mottled skin, the stroke reaction resulted in whealing in irregular areas corresponding to the mottling. This substantiates the findings of Sir T. Lewis, that the darker areas of mottling are relatively unresistant.

In whooping cough, the serum calcium is lowered, and this factor probably contributed to the tendency to haemorrhage. The child was treated with calcium lactate and at the end of 3 weeks whealing was very difficult to produce by stroking. The walls of the capillaries had become less permeable.

Erysipelas. In this condition there is a creeping inflammation with acute reaction maintained at its moving edge. The poison is introduced locally and is trapped in the skin. The marginal spread indicated that the stimulus to which the skin is responding is moving radially, and continues to act, releasing histamine as it moves.

Four cases of erysipelas were observed with special reference to the presence of histidin in the urine, and in each of the cases a strong positive was obtained. The deepest colour change being noted when the spreading stage was most marked.

In two of the cases, signs appeared in the chest, which suggested a commencing pneumonia, but these disappeared when the spreading infection of the skin was arrested.

Drs Dale and Laidlaw first suggested that histamine or some like substance might be responsible for the vasodilatation in muscles and glands during functional activity. It is a powerful stimulant of gastric and intestinal muscles and it may also act as the dilator of capillaries during digestion and in all organs during increased activity.

Applied clinically this appears to be true. The following observations support this view:-

(1) After a good meal, vasodilatation of the capillaries of the exposed parts of the body take place. If the blood pressure is taken just before, and then immediately following a meal, there is a decided lowering at the second reading.

(2) A great many asthmatics complain of a sense of fatigue, and shortness of breath for a short time after a meal. A large proportion of asthmatics can tell when an attack is coming on by a marked increase in their appetite. They state that a day or two before an attack, they never appear satisfied with an ordinary meal. If a good purge be taken, the impending attack often is avoided. Ivy and Jarvois (American Journal of Physiology 1925) demonstrated a definite stimulating effect of histamine and other amines on gastric glands, and also showed that free purgation

depressed the continuous flow of gastric secretion The toxic amines are probably formed in the large intestine and drastic catharsis would prevent their absorption, and so lessen the secretory action of the stomach.

(3) Asthmatics state that one or two days before the onset of menstruation (i.e. increased activity of the ovaries) some respiratory distress is the rule. Increased production of histamine affects the sensitive individuals.

(4) During pregnancy, asthmatics tend to have more frequent attacks. One woman who has had 4 children, only gets asthmatic attacks during her periods of gestation. The attacks begin just before the first missed period and continue all through. Immediately following delivery her respirations become free. Women who are liable to urticaria often get attacks just before or during menstruation, and during gestation.

(5) Increased functional activity due to pregnancy gives a fall in the blood pressure. The skin reactions are more marked. The flare is generally vivid and whealing takes place readily. Iminazolyl ring products appear in the urine. The bromine water test has been suggested as a test for pregnancy.

(6) Muscular exertion brings on an attack of asthma in many cases. This was well shown in the case

of a physical training instructor who suffered from asthma. He had wonderful muscular development and was able at will to throw almost any muscle into strong contraction leaving other muscles relaxed. His chest expansion was over 10 inches, which was obtained by throwing all the muscles round his chest wall into strong contraction. When demonstrating this he got a severe asthma attack and he stated that he had to give up his work because of the effect on his breathing.

SERUM CALCIUM AND HISTAMINE.

There appears to be a close relationship between the action of histamine and the calcium content of the blood. Meyer and Gottlieb (Experimental Pharmacology) state that withdrawal of calcium greatly increases the irritability of the vegetative nervous system. According to the investigations of Chiari and Januschke, the degree of permeability of the vessels and the process of transudation depends on the calcium content of the tissues. Increase of calcium content hinders the formation of transudates and oedema, while withdrawal of calcium increases it, and the reaction of the skin to inflammatory irritants depends on the same way in the calcium. In animals which have been treated with subcutaneous injections of calcium, and which are rich in calcium, the phenomena of inflammation, either do not occur, or are lessened. The conjunctiva does not react with marked hyperaemia, chemosis and pus formation, as it usually does to the instillation of oil of mustard. The pleural and pericardial exudations which are produced by many infections and poisonings are lacking, and the production of skin exanthemata and eczema is hindered or made more difficult. It appears as if the absorbed calcium had made the walls of the smallest vessels closer and less permeable for plasma and blood corpuscles.

The following experiments were carried out to test this:-

The scratch test as for protein sensitiveness was made using solutions of histamine and calcium lactate.

Five scratches were made A, B, C, D and E.

A. received solution of histamine.

B " " " calcium lactate.

C. " mixture of calcium lactate and histamine.

D. " first a solution of calcium lactate and at the end of 3 minutes, histamine was added.

E. Normal saline.

A. gave the typical flare and wheal.

B. and E. showed very little reaction. The calcium did not appear to increase or diminish the development of wheal formation.

C. developed at the same rate as A. showing that the calcium had no retarding effect on the action of histamine.

A solution of calcium lactate was next injected subcutaneously. At the end of 20 minutes, a scratch was made over the injected area, and a control scratch made at a distant part of the arm. Into both a solution of histamine was rubbed. Within 3 minutes the control scratch showed normal development of flare and wheal. No reaction was manifested in the scratch near the puncture. At the end of 10 minutes a slight flare began to show, and slight wheal formation was noted. At the end of 45 minutes a definite wheal had formed about half the size of the control scratch which by now was fading. At the end of 2 hours the control wheal had disappeared, while the one near the puncture was still well defined.

24 hours later, some thickening due

to unabsorbed calcium lactate could be felt in the tissues near the seat of injection and a repeat experiment was carried out. The inoculation over the injected area developed a flare and wheal in about 10 minutes against the control time of 3 minutes.

20 grs. of calcium lactate were taken orally 4 times a day for 2 days and on the 3rd, day a histamine scratch was laid down. The wheal developed in 5½ minutes, thus showing retardation of exudate.

These experiments confirm the statement of Meyer and Gottlieb that the presence of calcium hinders the development of wheale formation. The first scratch experiment show that the action of calcium takes longer than histamine, as there was no retarding effect when calcium and histamine were mixed.

A drop of 1:3,000 histamine solution instilled into the eye gives well marked dilatation of the arterioles of the conjunctiva, identical with the appearance of the eye at the commencement of measles.

After taking calcium for two days it was noted that instillation of histamine did not give rise to the same rapid development of hyperaemia though the injection of the vessels gradually became marked, but less than with the previous instillation before taking the calcium. The delay in the development of the hyperaemia was about 4½ minutes.

Another experiment was carried out

on a girl who was suffering from a chronic eczematous condition. A histamine scratch was laid down on her arm and a corresponding one was made on the writer's arm. Both developed normally. The patient was given calcium sulphide gr. ½ three times a day. At the end of a fortnight scratches with histamine were made as in first instance. The control scratch developed normally in about 3 minutes, while the scratch on the girl's arm showed very little reaction. At the end of 20 minutes a small wheal had developed about one third of the size of the Control. At the end of one hour it was fading, never having increased in size.

Having regard to these findings the serum calcium was estimated in a number of cases where the liberation of histamine was considered to explain some of the symptoms.

ESTIMATION OF CALCIUM CONTENT.

The method used was Collip's modification of the Kramer - Tisdall method for the determination of calcium in small amounts of serum. (Journal Biolog. Chemistry 1923 LV1 and 1925 LXIII)

(1) Measure into a graduated centrifuge tube
2 c.c. distilled water, 2 c.c. freshly separated blood serum to be tested, and
1 c.c. saturated aqueous solution of ammonia or potassium oxalate (potassium oxalate was used in this case)

(2) Mix thoroughly by rotating and flicking the bottom of the tube - Stand for 30 minutes and again mix.

(3) Centrifuge for 5 minutes at 1,500, or 3 minutes at 3,000 revs. per minute.

(4) Pour off and reject supernatent fluid, wiping the mouth of the tube and leaving the deposit intact at the bottom of the tube.

(5) Add 4 c.c. of 2% ammonia in water. Mix and centrifuge as before.

(6) Again decant supernatent fluid. Add 4 c.c. 2% ammonia. Mix and centrifuge as before.

(7) Decant off fluid and add to deposit 2 c.c. $\frac{N}{1}$ Sulphuric Acid. Mix and heat at 70° for 5 minutes or boil in water bath for 1 minute.

(8) Titrate resulting solution with $\frac{N}{100}$ potassium permanganate using a micro-burette until faint but definite pink colour is obtained persisting for 1 minute.

(9) Also estimate the amount of $\frac{N}{100}$ potassium permanganate solution used for 2 c.c. $\frac{N}{1}$ H_2SO_4 alone and subtract this amount of $\frac{N}{100}$ potassium permanganate from that used in test.

(10) Resulting number of c.c. of $\frac{N}{100}$ potassium permanganate multiplied by 10 gives number of milligrammes of calcium per 100 c.c. of blood serum tested.

e.g. Amount of $\frac{N}{100}$ KMn 04 used in test 1·18

Amount of $\frac{N}{100}$ KMn 04 ag. 2 c.c. $\frac{N}{1}$ H2S04 0·04

1·14

∴ Serum calcium in mgrms. per 100 c.c. = 11·4.

Normal blood serum contains 9·5 to 11·5mgms. of calcium per 100 c.c.

RESULTS.

Normal serum calcium is usually reckoned between 9·5 - 11·5mgrs. per 100 c.c.

Hendriks (Biochemical Journal XXIII No. 6) has shown that the above method generally gives somewhat higher results than several of the other methods used for calcium estimation.

The results obtained did not show any marked fall in the serum calcium, though all fall in low average group, and if the method used tends to give high readings, the findings indicate that in these cases, even a slight lowering of the calcium content may accentuate the action of liberated histamine, and so aggravate the symptoms due to histamine.

SERUM CALCIUM ESTIMATIONS.

NAME.	AGE.	DISEASE.	SERUM CALCIUM IN mgs. PER 100 c.c.
(1) Mrs. S.T.	28	Asthma	10·4
(2) Mrs. E.H.	32	"	9·9
(3) Mrs. F.C.	32	"	9·7
(4) Master I.B.	21	"	8·9
(5) Mrs. E.G.	36	"	8·6
(6) Mr. F.G.	40	"	9·6
(7) Mr. W.H.B.	38	Angio neurotic oedema.	9·8
(8) Mrs. S.	28	Epilepsy.	10·1
(9) Miss F.C.	25	Chilblains.	9·6
(10) Miss M.C.	23	"	8·8
(11) Miss E.S.	21	"	10·0
(12) Miss F.H.	19	"	9·4
(13) Miss A.C.	20	Asthma	10·7
(14) Miss F.H.	37	"	9·0
(15) Mr. W.F.W.	36	"	9·8
(16) Miss R.	18	Epilepsy	8·4
(17) Miss M.C.	22	Asthma	8·2
(18) Mr. W.D.	36	"	9·0

Histamine plays an important part in physiological and pathological conditions. What happens to it after it has produced its action is not known. Dr. Dale suggests that it is carried to the lungs where it is destroyed, thus explaining the large proportion of histamine found in the lungs.

Just as the removal of CO_2 from histidin converts a pharmacologically inert substance into a very active substance, so some further breakdown, reducing the toxicity, may take place. This was the reason why the bromine water test was carried out. The test is given for histidin, but it appears to be due to the presence of products of the iminazolyl type, and as such may be useful in explaining the fate of some of the histamine. If it is broken down, into some substance which still contains the iminazolyl ring, it may be excreted in the urine and so give a positive urinary test

HUNTER'S MODIFICATION OF THE KNOOP BROMINE WATER TEST FOR HISTIDIN. (BIOCHEM. JOUR. 16, 1922, P. 640)

Knoop 1908, adds bromine water to solution until there is just a slight excess. On heating, excess bromine disappears, and in presence of histidin a brownish red colour develops. The solution should be slightly acid. The test gives a positive with histidin in dilution of 1:1,000.

Hunter's modification gives positive with certainty at dilution of 1:10,000 and faint colour at 1:20,000.

Some urine which must be acid in reaction, is saturated with bromine water, and shaken up. If the urine is alkaline, dilute acetic acid is added till reaction is acid.

The excess bromine is extracted with chloroform. When, after repeated extractions, the super-natant fluid is colourless, a little is boiled in a test-tube for 2 - 3 minutes. Any colour change is noted. If no change takes place, the result is negative. If the solution gives a pink or brown colour, it is allowed to cool, and amyl alcohol added and thoroughly shaken up. If the colour is not extracted by amyl alcohol, the colour change indicates histidin. If extracted with amyl alcohol, the presence of tryptophane is indicated.

This test has been suggested as a test for early pregnancy, but its worth in that respect is of no value. While pregnancy does undoubtedly give a positive result in a fair percentage of cases, the large variety of conditions in which a positive reaction has been obtained makes the test of no diagnostic use.

This test was applied in a large number of cases, the object being to try to find out, if, in those conditions where there was evidence of a large liberation of histamine, any trace of a related amino-acid or its derivative could be found in the urine.

The action of heat on the skin is to liberate histamine, giving the flushing of the skin due to dilatation of the capillaries. The following personal experiment was carried out:-

After a hot bath which gave a good skin reaction, flushing of the exposed parts of the body was particularly noted. A specimen of urine was examined immediately following the bath and tested by the bromine water test, giving a strong positive result. A specimen obtained just previous to entering the bath was negative. The experiment was repeated after returning from a seaside holiday, during which a large area of skin surface was deeply sunburnt. The hot bath caused a more extensive skin reaction with a consequent greater liberation of histamine. The bromine water reaction being very much darker.

These experiments together with the experiment when histamine was injected into the body, show that some excretion, of a substance related to histamine takes place by the urine. Urine from a large number of cases of measles was examined for this reaction. At the onset of the disease the result is usually negative or very slight. As the lung symptoms develop, the colour changes become deeper, and disappear when the lung returns to normal. This appears to support the theory that histamine is carried to the lungs for destruction and as the involvement of the lung leads to diminution in its function, some other route of excretion is used, and a related substance is found in the urine.

In this connection, the results of the bromine water test in cases of lobar pneumonia are interesting. At the onset the reaction was negative. As extension and consolidation took place, and an increasing amount of lung tissue thrown out of action, the test became positive, and remained so till resolution, when it again became negative. Three cases only were observed in this way, but in each the results were uniform.

Deficient oxygenation of the blood during the invasion and consolidation stages would increase the acidity of the blood, and so tend to the liberation of histamine. This will be referred to later in reference to acute pulmonary oedema.

BROMINE WATER REACTION.

\- negative
\+ present but faint
\+ + definite
\+ + + very marked.

NAME.	SEX.	AGE.	DISEASE.	RESULT BETWEEN ATTACKS.	1ST. SPECIMEN AFTER ATTACKS.
E.T.	F	28	Asthma	-	+ +
J.C.	F	32	"	-	+
A.C.	F	20	"	-	+ +
M.G.	F	33	"	-	+
J.G.	M	43	"	-	+
M.P.	F	35	"	-	+ +

BROMINE WATER REACTION (continued)

\- negative
\+ present but faint
\+ + definite
\+ + + very marked.

NAME.	SEX.	AGE.	DISEASE.	REMARKS.	RESULT.
M.R.	F	43	Measles.	Rash well developed 1 week later, rash fading	+ + +

NAME.	SEX.	AGE.	REMARKS.	RESULT.
J.S.	M	38	(Before hot bath. (After hot bath.	- + +
J.S.	M		(Before hot bath. (After hot bath.	- + + +
J.S.	M		Before histamine injection. After histamine injection.	- + +

BROMINE WATER REACTION (continued)

- negative
+ present but faint
+ + definite
+ + + very marked.

NAME.	SEX.	AGE.	DISEASE.	REMARKS.	RESULT.
J.D.	M	8	Scarlet fever	2nd. day of rash. Rash nearly faded Desquamating end of 5 weeks.	+ + + + -
J.T.	M	6	" "	1st. day of rash. end of 1st week. end of 4th week.	+ + + -
T.T.	M	5	" "	1st. day of rash end of week.	+ -
J.R.	F	5	" "	2nd. day of rash. end of 1st week. end of 3rd week. end of 5th week. ending 6 weeks.	+ + + + + + + -
R.T.	M	12	" "	2nd. day of rash end of 1st week.	+ + -
J.B.	F	2 7/12	Measles	Koplik's spots present. Rash well developed Rash almost disappeared. Week after rash disappeared.	+ + + + -
E.O.	F	3	"	Rash well developed 1 week later, rash faded.	+ -
J.G.	F	3	"	Severe rash with bronchial complication. 3 days later - rash fading, chest clearing. End of 1st week, chest clear. End of 2nd. week, chest clear.	+ + + + + + -

BROMINE WATER REACTION (continued)

- negative
+ present but faint
+ + definite
+ + + very marked.

NAME.	SEX.	AGE.	DISEASE.	REMARKS.	RESULT.
B.L.	F	5/12	Teething	Bronchitis Next day - tooth erupted - chest clear.	+ + -
J.L.	F	7/12	"	Bronchitis Tooth erupted - recovery.	+ + -
B.M.	M	11/12	"	Severe Bronchitis next day 2 days later - chest clear - tooth erupted.	+ + + + + -
B.R.	M	10/12	"	Bronchitis Next day - tooth erupted	+ -
R.S.	M	1 2/12	"	Bronchitis Next day - chest clear.	+ + +
A.S.	F	11/12	"	Bronchitis 2 days later - recovery.	+ -
B.H.	F	1	"	Gastro enteritis	+
J.H.	M	6/12	"	Bronchitis 3 days later - Bronchitis still present. 1 week later - tooth erupted - chest clear.	+ + + -
B.F.	M	1 6/12	"	Diarrhoea 2 days later - Bronchitis 2 days later - Bronchitis 2 days later - tooth erupted	+ + + + + -
J.D.	F	10/12	"	Eczema - arms and legs and face. End of week - eczema worse 2 days later - eczema improving. Next day - skin improved - tooth erupted.	+ + + + + -

BROMINE WATER REACTION (contintued)

\- negative
\+ present but faint
\+ + definite
\+ + + very marked.

NAME.	SEX.	AGE.	DISEASE	REMARKS.	RESULT.
C.J.	F	4/12	Vaccination	7th. day. 12th. day 15th. day	+ + + +
R.B.	M	3/12	"	1st. day 7th. day 10th. day 14th. day	- + + + + + -
B.O.	M	4/12	"	1st. day 3rd. Day 7th. day 10th. day 14th. day	- + + + + + -
O.B.	M	7	Chicken pox	rash well developed. 1 week later - rash fading	+ + -
W.M.	M	6	Urticaria (green apples)	next day.	+ + -
J.F.	M	6	Erythema nodosum	1st. day of nodules 3rd. day 5th. day	+ + + + + -
J.P.	F	19	Gnat Bites	Extensive erythema of both legs round several gnat bites Next day.	+ + -

BROMINE WATER REACTION continued.

- negative
+ present but faint
+ + definite
+ + + very marked.

NAME.	SEX.	AGE.	DISEASE.	REMARKS.	RESULT.
G.L.	F	1 6/12	Superficial Scald both legs.	1st. specimen after accident. Next day. End of week.	+ + + + -
J.D.	M	54	Cerebral Haem.	Period of cyanosis Period of capillary dilatation.	- +
E.S.	F	28	Carbuncle	Severe reaction round developing carbuncle. Next week.	+ + -
J.H.	M	61	Erysipelas (face)	Spreading infection 3rd. day 5th. day improving 7th. day no further spread. 12th. day 14th. day - recovery.	+ + + + + + + + + + -
A.E.	M	28	" "	1st. day 2nd. day spreading 3rd. day still spreading. Anti-scarlatinal globulin given. 4th. day no further spread. 6th. day- recovery.	+ + + + + + + + + -

BROMINE WATER REACTION (continued)

- negative
+ present but faint
+ + definite
+ + + very marked

NAME.	SEX.	AGE.	DISEASE.	REMARKS.	RESULT.
M.J.	F	60	Lobar pneumonia.	2nd. day 4th. day 6th. day, crisis 8th. day	+ + + + -
J.D.	F	54	" "	1st day. 3rd day. 5th. day 7th. day - death.	- + + + + +
M.A.	M	28	" "	1st. day 3rd. day 6th. day 8th. day - crisis 10th. day	- - + + + + -

That there is a very close relationship has been proved.

(1) Subcutaneous injection of histamine is followed within 20 minutes by the appearance of a substance in the urine which gives the reaction.

(2) Liberation of histamine by action of a hot bath gives a strong positive reaction almost immediately.

(3) Positive reactions have been found in the following conditions, Measles, Scarlet Fever, Paratyphoid Fever, Erysipelas, Gnat Bites, Erythema Nodosum, Pneumonia, Teething disorders (especially Bronchial), immediately following asthma attack, severe scalding of the skin, angio. neurotic oedema, peptone injections, in all of which a considerable liberation of histamine takes place.

Since the investigation was carried out, some support seems to be given to it by the diazo-reaction results.

Ehrlich's diazo-reaction is obtained in typhoid fever, measles, typhus fever, scarlet fever, pneumonia, tuberculosis and erysipelas (Price's Practice of Medicine P. 71) and G. Hunter (B.M.J. 1922) showed that iminazole derivatives were primarily the cause of this reaction.

ALLERGIC DISORDERS.

It has been demonstrated that the condition of anaphylactic shock experimentally produced is analogous to certain types of asthma. Bronchial obstruction is a common factor. This obstruction may be due to-

(a) Spasm of the bronchial muscle.
(b) Swelling of the mucosa.
(c) Excessive bronchial secretion.

The nerve supply to the lung is through the vagus, supplying the broncho - constrictor fibres, while the sympathetic supplies the broncho-dilator fibres. Hyper-excitability of the vagus and para-sympathetic gives the condition known as vagotonia, as opposed to sympathetonus, stimulation of the sympathetic. Normally the sympathetic and parasympathetic are antagonistic, but their action is balanced.

The functional activity of the autonomic nervous system is closely associated with the endocrine glands - the thyroid, supra-renals, and pituitary and their secretions are increased by stimulation of the sympathetic; a diminution of their secretions is obtained by vagal stimulation.

Lack of balance may result if the vagus is powerfully stimulated, and the suprarenal and other endocrine glands are unable to mobilise sufficient internal secretion to keep the vagal action within normal limits, or diminution of the secretion of the suprarenal may allow unrestricted action of the vagus giving condition of vagotonia.

In asthma there is overaction of the vagus particularly that part supplying the respiratory tract. Anaphylaxis is also associated with vagotonia.

Fatigue, as a factor in explaining asthma, acts by exhaustion of the suprarenals, diminishing their internal secretion, and by so doing, increasing the activity of the vagus, while at the same time withdrawing the bronchodilator action.

Injection of adrenalin or fright (which stimulates the adrenalin output) will often cut short an asthmatic attack by increasing the broncho-dilator action of the sympathetic fibres. In sleep the parasympathetic gains control and this explains the frequency of nocturnal attacks of asthma.

To produce symptom - complex, two factors are necessary

(1) Basic toxic condition.

(2) Irritable nervous system.

It is a fortunate circumstance that only relatively small number of individuals are sensitive to certain substances, and while the end result is the same, in all cases, namely the liberation of histamine, this effect may be produced in a great many different ways.

Eppinger and Hess have described a number of symptoms which are attributed to the overaction of the vagus nerve - vagotonia, and their cases of asthma show the chief characteristics- namely, a tendency to urticaria, dermographia and eosinophilia.

The stroke reaction giving the "triple response" explains the condition of dermographia and it will be shown later that in the cases investigated and reported in this thesis, the skin reactions were often well marked.

In health the sympathetic and the parasympathetic are balanced. Practically all diseases tend to produce a disturbance in the balance. If the sympathetic is overstimulated we get a condition of sympathetotonus and if the parasympathetic is overactive, a condition of vagotonia is set up.

It would appear that a certain number of people have as their normal constitution an excessive activity of the sympathetic or the parasympathetic.

Stimulation of the sympathetic nervous system leads to increased secretion of adrenalin. Adrenalin and histamine are antagonistic in the same way as the parasympathetic and sympathetic are antagonistic.

Whether histamine stimulates the parasympathetic, and so produces a condition of vagotonia, or whether the stimulative of the vagus leads to increased liberation of histamine is not known, but of their close interrelationship there is no doubt.

The relationship between histamine and the parasympathetic, and adrenalin and the sympathetic appears to be the same.

That excessive activity of the parasympathetic is concerned in the production of asthma has been strongly suggested by the remarkable curative result of the subcutaneous injection of adrenalin, i.e. corresponding to the stimulation of the sympathetic nervous system. But it must be remembered that a disease is not always due to the absence of the remedy which relieves the symptoms. Other things may cut short an asthma attack e.g. Emesis, or injections of morphine, or atropine. In the case of endocrine disturbances such as theory is specially attractive.

Since the activity of the sympathetic is closely related to the output of adrenalin, insufficiency of the adrenal glands, by diminshing the tone of the sympathetic might lead to a relative vagotonia.

If this held good, subjects of Addison's

Disease in which the adrenalin content is deficient should be specially liable to manifestations of vagotonia. This is not so, and therefore relative vagotonia or adrenal insufficiency does not explain the condition.

An absolute vagotonia however, either inherited or acquired, may however explain why certain people only are hypersensitive to certain stimuli, endogenous or exogenous, which lead to the clinical manifestations of asthma, urticaria, or other allergic conditions.

In favour of this irritability of the parasympathetic may be mentioned the recognised hereditary factor in asthma. At present, the subject is difficult and it is safer to rest content with the view that in some cases an irritable vagus centre and in others a toxic idiopathy, or in some both may be present.

In asthma and allied conditions it is attractive to consider two etiological factors-

(1) The disposing condition of the Soil, vagotonia and hypersensitiveness to foreign protein.

(2) Exciting cause such as the particular protein or mechanical or physical stimulus but here again complications arise as the same factor may appear to set up both conditions.

Guttman - (Presse Medicale Paris 1923) records cases of asthma due to appendicitis and argues

that irritation of the terminal fibres of the vagus in the fibrotic appendix sets up Vagotonia, and that for the most part the familiar symptoms of appendix dyspepsia are those of vagotonia. In one case pressure over the appendix immediately brought on a paroxysm of asthma.

One of my cases of asthma, Mrs. G. aet 56, who suffered from gallstones, had an attack of asthma every time she had gallstone colic.

SKIN TESTING FOR PROTEIN SENSITISATION.

The diagnostic protein extracts used in these tests were supplied by Messrs. Parke, Davis &. Co.

Twentynine groups were used, representing 135 protein extracts, all the common food, bacterial, epidermal and pollen proteins being represented. If one group gave a positive reaction, careful history and experimental exposure and avoidance of the individual proteins in that group, will usually identify the particular offending substance. A control containing a base similar to that present in the diagnostic extracts was also used.

Technique. The skin usually of the arm, was cleansed with soap and water, dried and rubbed with alcohol, and then allowed to dry completely. Single scratches about 1 c.m. in length, made through the surface layer of the skin, not sufficiently deep to draw blood, were inoculated with a small amount of the test proteins, and rubbed in.

A positive reaction showed in from 3 to 20 minutes and was indicated by a well marked bright red "flare", and the development of a well defined urticarial wheal. The flare in a positive reaction extended usually 3-5 cm. on each side of the scratch, and the wheal was roughly oval measuring 2-2½ c.m. across and 3-3½ c.m. in long axis. The outline was irregular and pseudopodic in appearance. When comparison was made between a "positive" and a scratch inoculated with histamine, the results were found to be identical.

ASTHMA.

- absent
+ present
+ + well marked.

"TRIPLE RESPONSE" after 5 strokes.

NAME.	SEX.	AGE.	PROTEIN SKIN REACTION.	TACHE.	FLARE.	WHEAL.
1. E.T.	F	28	Hay pollen + +) Milk + +)	+	+ +	+
2. W.T.	M	22	Milk + + +	+	+	+
3. K.J.	M	61	Potato + +) Bacteria + +)	+	-	-
4. A.M.T.	F	24	Pollen +	+	+	-
5. J.R.	M	38	None	+	+	-
6. G.W.	M	46	Bacterial +) Pollen +)	+	+ +	+ +
7. F.C.	F	32	None	+	+	-
8. A.B.	F	28	Beans + +	+	+	+
9. F.H.	F	37	None	+	+	-
10. F.C.F.	F	32	Potato +	+	+	+
11. F.G.	M	40	Epidermal + +	+	+ +	+ +
12. I.B.	M	21	Epidermal + +	+	+	+
13. A.C.	F	20	Epidermal + + +	+	+ +	+
14. W.Y.	M	56	Oats pollen +) Milk + +)	+	+ +	+

over.

ASTHMA (continued)

- absent
+ present
+ + well marked.

"TRIPLE RESPONSE" after 5 strokes.

NAME.	SEX.	AGE.	PROTEIN SKIN REACTION.	TACHE.	FLARE.	WHEAL.
15. M.C.	F	33	Eggs +) Feathers + +)	+	+ +	+
16. A.D.	M	20	None	+	+	-
17. A.E.S.	M	26	Epidermal + + (cat and dog)	+	+ +	+ +
18. F.S.	M	28	Epidermal + + (cat and dog)	+	+	+
19. F.T.	F	24	None	+	+	-
20. E.G.	F	30	Pollen +) Fowl + +)	+	+	+
21. E.A.	F	7	Fowl + +) Milk +)	+	+	+ +
22. M.A.	F	32	Milk +) Beans +)	+	+ +	+
23. M.P.	F	46	None	+	+	-
24. S.G.	F	34	None	+	+	-
25. J.C.	M	68	Feathers + +	+	+	+ +

BRIEF NOTES ON ASTHMA CASES WHICH GAVE POSITIVE SKIN TEST WITH DIAGNOSTIC PROTEINS.

(1) E.T., F. 28. Hay Pollen + + Milk + +

Duration 11 years. Worst attacks June and September (pollen.) Milk always upsets her - has avoided milk all her life. Peptone injections - slight relief - not so short of breath - usual slight attacks pass off quicker since injections.

(2) W.T., M. 22. Milk + + +

Asthma since child - had noticed that milk made very ill, took as little milk as possible. Peptone injections - marked relief - states never felt better.

(3) K.J., M. 6½. Potato + + Bacterial (Friedlander Mic. Catarrhalis) +

Following pneumonia 3 months old. Very enlarged tonsils - since removed. Potato never suited him.

(4) A.M.T., F. 24. Hay pollen +

12 years duration - June and September worst months. Peptone injections - no attack for 2½ years.

(6) G.W., M. 46. Bacterial (Friedlander Mic. Catarrhalis) + Pollen +

Chr. Bronchitis - worse attacks in summer.

Peptone no benefit - ephedrin hydrochloride gives great relief.

(7) H.B., F. 28. Beans + +

Worst attacks August and September. Meal of "runner beans" before each severe attack - skin reaction very

marked. Experimental avoidance and taking beans confirmed the hypersensitiveness to beans.

(10) F.C.H., F. 32. Potato +

Onset 5 years ago. Has noticed that potato disagreed, and discontinued them 2 years ago - subject to urticaria.

(11) F.G., M. 40. Epidermal + +

Army Gymnastic Instructor - wonderful muscular development - chest measurements - inspir. 51⅝" expir. 41" Expansion 10⅝". Antrum disease 1914. Asthma started 1917. Antrum still draining slight exertion brings on attack - if he throws a group of muscles into strong contraction, asthma comes on. Wet dog or steaming horse gives attack at once. Ephedrin gives great relief.

(12) I.B., M. 2½. Epidermal + +

Gets asthma after playing with dog or cat. Chocolate often brought on attack.

(13) A.C., F. 20. Epidermal + + +

Onset at age of 12. Horse hair covered couch removed from room, marked improvement. Stated peptone injections did her more good than anything she had had previously.

(14) W.E.,M. 56. Oats pollen + Milk + +

Duration 23 years. States milk "always makes bad" attacks generally between 3 a.m. and 5 a.m. regularly.

Autumnal attacks regularly, - Oats pollen.
Peptone - states marked improvement - unusual to get a bad night.

(15) M.C., F. 33. Egg + Feathers + +
Duration 3 years. Slept on feather bed - and feather pillows. Egg gives "bilious attack", followed by asthma; she had discontinued egg 2 years ago.

(17) A.E.S., M. 26. Epidermal (cat and dog) +
Dog and cat kept as pets. These destroyed - careful avoidance led to improvement. Peptone injections very great relief - never felt so well all his life, can walk distance without fatigue - slept well since 2nd. week of injection - before injection hardly had a good night's sleep.

(18) F.S., M. 28. Epidermal (cat, dog and horse) +
Pit pony driver. Peptone gave marked relief.

(20) E.G., F. 36. Pollen + Fowl + +
Onset 1921, subject to urticaria - usual time of attack 2 a.m. - most severe attacks during summer - especially hot summer day - can take fowl without feeling ill effects.

(21) E.A., F. 7. Fowl + +
Daughter of 22. Asthma since whooping cough 8 months ago. Chocolate brings on attack. Never

been upset following meal of fowl.

(22) M.A., F. 32. Milk + Beans +

(Sister of 7) Asthma started after birth of No. 21. Chocolate made very sick during whole period of gestation. No ill effects from milk or beans.

(25) J.C., M. 66. Feathers + +

Slept on feather bed. When all feathers, pillows and bed, removed from house, no more attacks.

SUMMARY.

No. of cases	25
No. sensitive to particular protein	18
No. showing no reaction.	7
No. sensitive to two groups.	7

TABLE SHOWING NUMBER OF CASES SENSITIVE TO PARTICULAR PROTEIN.

Protein	Pollen	Epidermal	Feathers	Bacterial
No. of cases	5	5	2	2

Protein	Milk	Potato	Egg	Fowl	Bean
No. of cases	4	2	1	2	2

"TRIPLE RESPONSE"

Tache	Flare			Wheal.		
+	+ +	+	-	+ +	+	-
25	8	16	1	5	11	9

ASTHMA AND PROTEIN METABOLISM.

Experimental evidence has been given to show that certain proteins taken in food may break down into toxic substances which have been proved to give rise to anaphylactic shock and asthma.

The regulation of diet in some cases of asthma is an essential in treatment. In those cases which have been found to be sensitive, avoidance of the specific protein almost invariably leads to absence of asthmatic attacks. The hypersensitiveness, however, usually persists and attacks may recur later if the patient is exposed to the particular protein.

Desensitisation of the patient by repeated small injections of the offending substance had been tried with considerable success in a number of cases. The patient gets a mild anaphylactic shock with each injection and so builds up an immunity. Witte's peptone, which contains a small amount of histamine, has given good results in certain cases. During the past year, a series of asthmatics were given gradually increasing doses of 7½% solution of Peptons (Armour's) Injections were given every four days, starting with ·5 c.c. and increasing by ·2 c.c. at each injection until the dose reached 2 c.c. After 6 full doses the course was discontinued.

Fourteen patients were treated in this way and the results have been surprisingly good. Two failed to get any benefit whatever. Two stated that they felt

better, though they still had attacks which were not so severe as usual. All the others derived great benefit, and stated that they had never felt so well since the onset of their asthmatic attacks.

Actinotherapy and heliotherapy have been used in treatment of asthma.

All these injection treatments and light treatment have as the underlying principle, the liberation of histamine in small doses in susceptible individuals, so building up a resistance.

ACUTE PULMONARY OEDEMA
AS A MANIFESTATION OF HISTAMINE SHOCK.

This distressing condition - commonly termed cardiac asthma and consisting of paroxysmal acute dyspnoea, generally occurring at night, or following exertion or unwonted excitement - may last from minutes to hours. There is a sense of suffocation, wheezing and coughing, with frothy sputum which may or may not be blood stained. The pink foam issuing from the nose and mouth during an attack is characteristic. Physical examination reveals wheezing respiration and bubbling râles, but auscultation is difficult because of the distress of the patient.

The disease is usually associated with high blood pressure and heart disease. The exciting cause is often obscure - a heavy meal, excitement, or the administration of an anaesthetic. In some cases, it may be a manifestation of angioneurotic oedema. In other cases, a failure of the left ventricle while the right contracts forcibly, may be the cause. Syphilitic heart disease, and chronic nephritis are the commonest predisposing conditions.

Palmer and White (Journal of American Med. Assoc. February 1929) give a review of 250 cases. They subdivide as follows:-

Total cases	250	in 3100	Heart cases		8%
Arterio-sclerotic-hypertensive Type	187	" 1736	"	"	10.7%
Syphilitic Heart disease	34	" 161	"	"	21%
Chronic nephritis	29	" 153	"	"	19%

Aortic regurgitation was the commonest valvular lesion, chiefly syphilitic, and mitral stenosis was infrequent. Signs and symptoms of well marked congestive failure make the prognosis grave. Coronary occlusion, leading to more or less chronic congestive failure of varying degree, punctuated by attacks of cardiac asthma, is common. Various theories have been adduced to explain this condition. Romberg's theory of initial inciting cause is that, with the coronary circulation narrowed by sclerosis, the blood pressure falls during sleep and becomes too low to force sufficient blood through the narrow coronary arteries. This partial occlusion of the blood to the ventricular muscle leads to acute failure and cardiac asthma. Wasserman ascribes the cause to a possible "cardio-aortic-bulbar-pulmonary reflex phenomenon".

Fraser (Lancet 1927-3rd Goulstonian Lecture) argues that increased respiratory effort in presence of mechanical difficulties, or in response to stimulation from respiratory centre, causes increased blood flow. The right ventricle responds more vigorously than the left, and the blood flow is increased through the pulmonary circuit. The left ventricle is unable to deal with it, and oedema results.

Ten cases of acute pulmonary oedema are here described. In all the cases except two there was serious

strain on the heart from intrinsic cause, coronary disease or aneurysm, or extrinsic cause, hypertension. Signs of heart failure were frequent. The attacks almost invariably came on in the middle of the night when the patient was recumbent, or else after or during excitement, i.e. when the blood flow was increased and extra work was thrown on the heart.

During sleep if, from left ventricular strain or failure, the right ventricle supplies more blood than the left ventricle can take care of, a gradual accumulation of blood takes place in the lungs, and the patient is awakened. By sitting up, some of the strain and stasis is reduced and recovery may take place.

The exact mechanism is not clear, but a comparison with the action of histamine suggests a probable explanation. In cardiac cases, the oxygenation of the blood is interfered with. The acidity of the blood is raised, and the reactive "buffer action" of the amino acids comes into play. This will lead to the appearance in the blood of substances of the histamine type. The animal experiments of Drs. Dale, Bayliss and Cannon support this view. Normally, the histamine liberated is balanced by the secretions of the adrenals, pituitary and thyroid. Excessive liberation of histamine may overcome the restraining influence of the sympathetic nervous system. During sleep, also, the parasympathetic is in control, and this affords an explanation of the nocturnal occurrence of the attack.

At the onset, the patient is collapsed - skin moist, clammy and feels cold - dyspnoea is marked, and gradually the cyanosis becomes deeper. If the patient is propped up in bed and hot foments applied over the heart, the colour may improve, the skin feel warmer, and in a few minutes a vivid red flush appears all over the face and exposed areas. This appearance is similar to the effect of injecting histamine. The blood pressure falls, and soon bubbling râles are heard all over the chest. This series of changes was repeatedly noted in the case of Miss J. (Case No. 3) and once in the case of Mrs. B. (Case No. 4)

A similar series of changes was noted in the following case of Cerebral hemorrhage:-
Mr. L.D. aet 54, had a cerebral hemorrhage which caused left sided hemiplegia. For the first two days he lay comatose with no return of consciousness. The cyanosis became very marked. On the third day the cyanotic appearance changed to one of intense flushing of the skin- dilatation of the capillaries - and the chest became full of bubbling rales. The blood pressure fell from $\frac{180}{100}$ to $\frac{120}{60}$. The variations in the skin colour were alternately cyanosis, and vivid flushing. The urine was examined by the bromine water test and during the cyanotic periods gave a negative result, but became positive in specimens obtained very soon after the periods of vivid flushing.

Cases of heart disease have a rich supply

of histamine. If the stroke reaction be tested for, whealing takes place readily, and the flare is usually marked. In a series of ten cardiac cases examined every one showed a marked reaction, the flare developing rapidly and whealing following one or sometimes two strokes. Never more than two strokes were necessary to produce a wheal.

RECORD OF CASES OF ACUTE PULMONARY OEDEMA.

No. 1.

Mrs. L. Widow, aet 46, 4-para.

FIRST ATTACK April 10th, 1923, - correcting one of her children - felt choking sensation in throat - When seen, dyspnoea very marked - She was collapsed - skin was cold and clammy - pink froth issuing copiously from nose and mouth - râles all over chest - looked like dying. Morphin. sulph ¼ gr. and atropin. sulph 1/100 gr. given hypodermically. In about 20 minutes, breathing became easier. Next morning, chest clear. The patient stated that she felt better except for general tiredness, but she had no recollection of the attack. Examination of the heart revealed a soft mitral systolic murmur, but she had no symptoms of heart disease. Blood examination was refused. (A year later her child aged 1½ was sent to hospital suffering from enlargement of the liver and spleen. Wasserman reaction was + +)

2nd. ATTACK June 14th, 1923, 11-30 p.m., - went to bed at 10 p.m., feeling well - found by one of the children - condition same as before and rapid recovery took place with atropine and morphine. She was given 1 hypodermic tablet each of morphia gr. ¼ and atropin. gr. 1/100, which she kept beside her, and instructions were given to the elder members of the family that, at the first onset, these were to be placed under the tongue.

Five attacks were similarly treated.

6TH. ATTACK, October 6th, 1923 - excitingly arguing with her next door neighbour when attack came on. I was

visiting in the same row of houses, and had the opportunity of following the attack from the onset. Breathing was difficult. Inspiration free at first, and expiration laboured (as in ordinary asthma) In about two minutes, gurgling commenced in the throat, and clear foam was blown out with difficulty. The dyspnoea was rapidly becoming worse. Face became blue and then ashen, showing up distended venules of the cheeks. In the excitement of the moment, she was given apomorphine hydrochlor. instead of morphine, and immediately she became very sick and this had the effect of instantly clearing the throat and mouth of foam. Atropin gr. $\frac{1}{50}$ was then given. The sickness stopped, and the patient went into a quiet sleep. Next day, she was very much better, and in fact stated that she had recovered quicker from that attack than from any previous one.

Injections of apomorphine followed by atropin gr. $\frac{1}{50}$ were used in subsequent attacks with marked success.

As time went on, the attacks became more frequent, coming in generally in the early hours of the morning, or if she had a little extra excitement. The heart condition never appeared to get worse. Incontinence of urine was present during each attack.

In all, she had 24 attacks before the fatal one which was very rapid in its course. The total period from the first onset to last was 2 years and 9 months.

A typical case of acute pulmonary oedema is here described - the cause being syphilitic. The treatment of this case by apomorphine is not one which could be adopted in many cases of acute oedema. Unless the heart muscle was of good tone, the apomorphine would probably hasten the fatal issue.

Case No. 2. Mrs. F. aet 36. Nullipara.

Seen at 2 a.m. for a neighbouring practitioner by whom she had been treated for several years for "heart trouble"

Her doctor stated that she had had several miscarriages and had aortic incompetence. Wasserman reaction had not been done. She had gone to bed in a condition of nervous exhaustion due to sudden reception of bad news.

The respiratory distress was marked, and pink froth came from nose and mouth. Atropine sulph. gr. $\frac{1}{50}$ and morph. sulph. gr. $\frac{1}{4}$ hypodermically caused rapid improvement.

In this case history suggested syphilitic heart disease - while the inciting cause was excitement leading to exhaustion of adrenal output, and deficient oxygenation leading to uncounteracted liberation of histamine.

Case No. 3. Miss J. aet 69, Coronary Disease - Myocarditis.

First attended with bronchopneumonia. Recovery left the heart weak. The heart sounds were very faint, and her exercise tolerance poor. Shortness of breath marked on slight exertion. 2 months later she had sudden acute pain over the sternum - resembling gallstone, colic - collapse - irregularity of the heart and aggravation of lung condition - signs of congestive heart failure were present. This attack was attributed to coronary disease, and her subsequent condition supported this. She became subject to attacks of acute pulmonary oedema. The attacks usually came on at night, and as a routine she was given atropine sulph. $\frac{1}{100}$ gr. every night. This somewhat lessened the frequency. It was noted that marked variations of the colour of her skin took place. Sometimes she would be blue and cold, with distended veins showing over the cheeks. At others, she would have a vivid red flush and the skin felt warm. The periods of cyanosis always preceded the red flushes, and can be explained by the marked cyanosis due to failure of the heart leading to deficient oxygenation, and the liberation of histamine. The injection of adrenalin gave temporary relief. These attacks were accompanied by a marked fall in blood pressure. On one occasion I had just measured the blood pressure when she began to have an attack. She was lying flat in bed, breathing became laboured, the pulse could hardly be felt, cyanosis became deeper. She was propped up in bed and hot foments

were applied over the heart. In 2-3 minutes she showed signs of recovery. Her colour changed, and her face was suffused with bright red blood. The blood pressure was noted. 8 minims of 1/1,000 adrenalin were slowly injected subcutaneously. The chest was examined, and there was a definite increase in the moist sounds from what had been present ½ hour previously.

B.P. Readings.	Before attack.	after signs of recovery.	after adrenalin.	next day.
	175/100	105/60	140/80	165/95
During a subsequent attack		100/65		160/98

Death took place from congestive heart failure - oedema of limbs and lungs. The nurse stated that at each attack, the bladder had emptied involuntarily.

A case of myocardial disease associated with coronary disease is here recorded, showing features suggestive of the action of histamine.

Case No. 4. Mrs. B. aet 63.

Hypertensive - arterio-sclerotic type. First seen 1-30 a.m. severe dyspnoea - pink froth issuing from nose and mouth. Heart sounds weak-marked flushing of the face. Atropine and morphine given, and recovery took place. No inciting cause could be elicited in this attack.

Examination next day showed high blood pressure 195/120 and she complained of giddiness and shortness of breath. Albumin was found in the urine.

One month later, 2nd. attack, 1 a.m., similar to first. Inciting cause was her daughter's wedding on the previous day.

One week later, 11 a.m. B.P. $\frac{200}{130}$-dyspnoea gradually getting worse - some oedema of hands and feet.

Same day 11-45 p.m. similar attack to previous two, face very flushed. B.P. $\frac{90}{50}$ collapsed, râles present in chest, pink froth from mouth. 1½ pints blood removed by venesection. Atropine and morphine given. Next day her blood pressure was $\frac{130}{85}$ and on succeeding days it rose gradually to $\frac{150}{90}$ and $\frac{180}{100}$ respectively.

At 3-15 p.m. of the 4th day, she had a cerebral haemorrhage which was fatal.

This is a case of acute pulmonary oedema in a hypertensive patient, and shows the marked fall in blood pressure during the acute attack.

Case No. 5. Mrs. N. aet. 65, 6-para, Hypertensive type-endocarditis.

Own blood - ve. The family history is indicative of syphilitic disease.

Girl aet 17, Palatal paralysis Wass + +
Girl aet 14, Deafness Wass. + +
Boy aet 7, Interstitial Keratitis.

First and fatal attack, 11-30 p.m. - went to bed at 10 p.m. feeling well - and after a hearty supper. The attack was typical and death took place within an hour.

Case No. 6. Mr. Wm. Mc. D. aet 69, Aneurysm of aorta (transverse arch)

Aortic systolic murmur - stridor - brassy cough - tracheal tugging were the dominant signs. During the last two weeks of life, he had repeated attacks of acute pulmonary oedema - at first one every other day and becoming more frequent - until he had several in one day. Morphine and atropine gave temporary relief. Phases of cyanosis preceded the acute attack and it is probable that reflex irritation of the vagi, set up a condition of vagotonia, while the deficient action on the failing heart caused deficient oxygenation and liberation of histamine.

Case No. 7. Mr. W.H. aet 66.

Hypertensive arterio-sclerotic alcoholic.

Chronic Bronchitis 18 months previously. His daughter states he had been well, and only complained of shortness of breath on exertion. Occasionally he had stabbing pains over his chest. Day before death, he was better than he had been for a long time - enjoyed his meals, and after a good supper of bread and cheese and 2 pints of ale, he went to bed at 9-30 p.m. At 12-45 a.m. his daughter was awakened by hearing a "peculiar gurgling" noise in her father's room. She found him half sitting up in bed, gasping for breath - there was a "rattling noise" in his throat, and frothy mucus was expelled from the mouth with difficulty. Death took place at 1-15 a.m.

Post mortem examination - lungs heavier than normal - sodden - and pinkish fluid could be expressed from the cut section of the lung.

Liver - Hobnailed-alcoholic cirrhosis.

Heart - Two old infactions were present, in the wall of the right ventricle. The coronary arteries were hard and calcareous. Atheroma of aorta was present.

I am indebted to Dr. R.G. Bradford, Brownhills, for permission to publish this case of his.

Case No. 8. Mrs. A.C. 56, Myocardial Disease. Breathlessness on exertion - cardiac area of dulness increased especially to the right - 1st. sound prolonged, 2nd. sound accentuated and reduplicated. Liver enlarged, and felt 1" below ribs on right side. P.R. 110 Faint trace of albumin in urine, B.P. $\frac{220}{150}$.

Injection of ergamine acid phos. containing 1 mgr. histamine given intramuscularly. Within a minute, the patient suddenly sat up in bed gasping for breath - vivid flush over face, pulse became very rapid and in about 2 minutes could hardly be felt. Bowels and bladder moved: Respiratory distress was most marked on expiration. The condition took ½ hour to subside.

A case is here recorded in which the injection of histamine in a cardiac case gave a condition, startlingly sudden in its onset, and in severity, very similar to the clinical cases of acute pulmonary oedema already recorded. It is included here in support of the theory that the mechanism of acute pulmonary oedema can be explained on a histamine basis.

Cases 9 and 10

Two cases of sudden death in children aged 3 and 5 respectively at the end of eruptive stage of measles are included in this series of cases of acute pulmonary oedema.

The first, aged 3, was seen for the first time at 11-45 p.m. The mother stated that the child had measles, and was apparently going on all right. The rash was clearly visible and appeared to be beginning to fade. The child suddenly became acutely ill at 11-30 p.m., gasping for breath, and appeared to be suffocating. Râles were heard all over the chest, and frothy mucus was present in the mouth. No signs of consolidation of the lung was present. The child died in half an hour.

The second child, aged 5, was visited daily for four days. On the first day, the conjunctivae were injected and Koplik's spots present in buccal mucous membrane. The rash was present on the 2nd. day, well developed on the 3rd. day, and at 1 p.m. of the 4th day, was beginning to fade. There was no sign of bronchial complications, and the child appeared to be progressing favourably. At 5 p.m. of the same day, an urgent message was received, and on visiting the house, the child was found to be very ill. The mother stated that at about 4-30 p.m., the breathing suddenly appeared to get laboured. Crowing was remarked, and rapidly the distress grew worse. The chest was now full of bubbling rales, and some frothy

sputum was expelled with difficulty. Death took place within an hour of the onset.

The diagnosis made at the time of death was acute oedema of the glottis, but recent work has suggested that this not infrequent tragic complication of measles, is of the same nature as acute suffocative pulmonary oedema and is a manifestation of histamine shock.

Clinically the condition resembles the suffocative stage of acute diphtheritic inflammation of the throat. Swabs taken were negative for diptheria but showed streptococci.

Three further cases have recently been observed in which at the end of the fading stage of the rash acute dyspnoea supervened. In two cases tracheotomy was performed and this gave temporary relief only, both terminating fatally.

MEASLES. In the ordinary routine of general practice, one frequently meets with a large number of pathological changes for which formerly no reason could be given. The discovery of the actions of histamine has helped to elucidate some of these problems.

Following on Lewis' skin researches, it can be accepted that histamine or some other substance readily yielding histamine can be released as a result of various stimuli-thermal, light, injury, exogenous and endogenous toxins - and if the defensive mechanism which regulates the supply of histamine breaks down, one may expect to get a general disturbance, owing to excessive liberation of histamine.

In the case of measles, the local skin manifestations - bright red rash - are due to histamine. There is vaso-dilatation with increased permeability of the capillary walls, and usually some stimulation of smooth muscles leading to gastro-intestinal disturbance. The eye symptoms are also similar to the instillation of histamine into the eye. Conjunctivitis is one of the earliest signs.

Incontinence of urine is also very common during the acute stage of the rash. In a few days from the appearance of the rash, usually some bronchial involvement occurs - severe coughing with râles all over the chest. The respiratory rate is increased often to 70 - 80 per min. The patient looks ill, often a diagnosis of acute bronchitis is made, and one anticipates a severe broncho-pneumonia. Frequently however, a remarkable change

takes place with a speedy recovery and sudden disappearance of the lung signs. The patient in the course of a day returns to a condition of comfort. This dramatic change could not be explained if the lung conditions were regarded as an acute bronchitis. The suggestion now made is that the skin eruption is a histamine response to infection, and that the histamine liberated in the skin is carried to the lungs where a condition, similar to the findings in animal experiment, leads to broncho-spasm, increased permeability of capillary walls, and excessive secretion. With the cessation of the skin supply of histamine which takes place when the rash fades, the lung condition disappears..

Mrs. R. aet 38.

MEASLES IN CASE OF HYPERPIESIS.

This patient has been attended for high blood pressure. When first seen it was $\frac{160}{115}$. After treatment it was reduced to $\frac{140}{105}$. An attack of measles supervened. When the rash was at its height, the blood pressure was $\frac{118}{86}$. The patient complained of giddiness and depression. She fainted several times during the day. Respiratory and pulse rates were increased. A histamine scratch test showed a very rapid development of the wheal due to adding histamine to an area which was liberating the same substance. A scratch repeated a week after the rash had faded gave a slower development, the difference being about 1½ minutes. As the rash faded, the blood pressure steadily rose till it was nearly at the former level.

No chest complications were remarked. During the eruptive stage, marked frequency of micturition was noted. This gradually passed off as the rash faded.

TEETHING DISORDERS.

In dealing with children's diseases in the first few years of life, a common explanation of certain ailments is "Teething" "The child cut every tooth with Bronchitis" or, "Every tooth caused sickness and diarrhoea" are commonplace remarks. Dr. R. Hutchinson in his Lectures on Diseases of Children says "You will find children who get an attack of bronchitis every time they cut a tooth. Why that should be, I do not know. Some people say it is produced in some mysterious reflex fashion, but I think that it is more likely that the teething simply lowers the resistance, like any other agency, and so renders it specially liable to suffer from chill"

A young child is often brought to the surgery with every sign of acute bronchitis. It looks very ill, and when it is visited next day with the expectation of finding a case of broncho-pneumonia, the child has recovered. This is a fairly common experience. The dramatic change is most striking, and the explanation is afforded by the analogy of the condition to histamine shock. If the mouth is examined carefully, a very fiery inflamed gum is seen stretched over an erupting tooth. The irritation caused by eruption of the tooth liberates histamine in considerable quantities. The systemic disturbance depends on which part is specially affected. If the bronchial tract, then one gets bronchitis and a condition resembling asthma. If the main action be an intestinal one, then sickness and diarrhoea are manifested owing to enterospasm and colitis. When an eczematous

condition of the skin is present at the same time as the tooth erupts, an exacerbation of the sore appears. The affected area looks more angry and fiery due to increased dilatation of the capillaries. Sixty cases of infants during teething were observed and the urine examined for the presence of histidin. The following conclusions were arrived at-

Simple eruption of a tooth with no systemic disturbance gave a negative Urinary Knoop's Test. If lung symptoms were marked, the urine gave a positive reaction; and remained so until the tooth erupted, when the lung symptoms rapidly disappeared and the urine became negative. Where gastro-intestinal symptoms were predominant, the urinary test was usually negative. Where a positive result was given, it was very faint.

M.F. aet 44, Housewife.

PLANT HYPERSENSITIVITY.

Eczema of both forearms recurred every spring since patient moved to a new home 3 years previously. After considerable time, the cause was found in the greenhouse - Primula obconica. She had personally attended to flowering plants when in the house, and the appearance of the rash corresponded with the presence of these plants. The rash began as an erythematous condition going on to wheal and bullous formation, and was most marked on the back of the wrist and fingers. Experimental avoidance of these plants till recovery took place, and then the development of the typical symptoms on exposure, confirmed the diagnosis. She decided to dispose of all the plants of this group, and assisted a friend to carry the plants from the greenhouse to the car. Next day she had her last attack of the rash. By careful avoidance of this particular plant, she has kept free for several years.

CHOCOLATE HYPERSENSITIVITY.

It has often been noticed that urticaria in children and adults often could be traced to chocolate. Several cases of asthma in children were also ascribed to chocolate. In one case of a boy aged 5, the parents stated that the attack almost invariably came on every Saturday night. Careful watch was kept on his diet and eventually chocolate was suspected. The mother stated that it was customary to give the boy a bar of Cadbury's Chocolate every Saturday afternoon. This was stopped, and the asthma attacks ceased. After 4 weeks freedom from the attacks he was given his usual bar of chocolate, and that night he had an attack. This experimental withholding and exhibition of chocolate was repeated on 3 occasions and each time asthma followed the taking of the chocolate.

Skin reactions to diagnosis proteins were all negative. Watery solutions of 4 brands of chocolate were used, and the only positive was to Cadbury's. This was not marked butaquite definite wheal was produced.

Great difficulty may be experienced sometimes in fixing on the offending substance. The following case of a lady who suffered frequent attacks of urticaria illustrates this point:-

The condition had been present for several years. Various articles of diet were suspected. It was noticed by keeping a detailed record of everything taken, that

chocolate was probably the offending substance. Abstinence from chocolate resulted in no urticaria. Chocolates were taken, and no urticaria appeared, thus chocolates were thought not the cause. Chocolates were continued and very soon urticaria appeared. Further investigations took place, and again chocolates became suspect. The question of a particular brand of chocolate was next thought of, and Fry's, Terry's, Kunzle's Chocolate were given without urticaria. Everytime Cadbury's Chocolate were taken extensive urticarial rash appeared within a few hours. Avoidance of Cadbury's Chocolate stopped any further attacks.

Skin tests using watery solutions of various brands of chocolate were used. In the case of Cadbury's Chocolate, the flare and wheal was present, but the reaction was a mild one.

The "triple response" gave whealing with five strokes.

Miss W.B. 20, Aspirin sensitive individual - seen first at 11-45 p.m. Patient collapsed, tachycardia - pulse very feeble, B.P. $\frac{100}{60}$ She had vomited shortly before. History - had taked 2 "Express Powders" which contained Aspirin and Phenacetin for the relief of dysmenorrhea, just before going to bed - in about 10 minutes she stated she felt a hot flush spread over her face, neck and hands, and later became sick, and then lost conciousness. Next morning she was perfectly well.

She had taken 2 "Express Powders" for the first time 1 month previously, and had suffered no ill effect. This was probably the sensitising dose, so that the second administration of the same led to a condition resembling anaphylaxis.

Skin reactions to various foreign proteins were negative - skin reactions to "Express Powders" did not give a definite positive result - the slight increase in wealing was not diagnostic. The bromine water test was positive in first specimen obtained after the attack.

The stroke reaction obtained after the attack gave a well defined "triple response" with 2 strokes.

The patient stated that she was very susceptible to gnat bites - extensive blistering resulting every time she was affected.

I.G., man aet 50, miner, Hypersensitive to iodine and Pot. iodide.

10. 11. 24, attended surgery with synovitis (knee) painted with Tr. iodi fort.

11. 11. 24, severe local reaction with acne-like spots over painted area and redness of skin of leg from groin to ankle - complaining of cough.

12. 11. 24, weeping eczematous condition over painted area, leg swollen and looked fiery, - signs of acute bronchitis T. 102°, P.R. 100.

12. 11. 24, local condition of leg very much better - cough better - chest clearer.

June 1925. Received a small cut on scalp while at work - painted with Tr. iodi mit. When seen next day T. 103°, delirious - face swollen resembling erysipelas - eyes closed - acute bronchitis - man looked very seriously ill out of all proportion to the small wound on scalp. After 3 days in bed recovered completely.

July 1926. Came to surgery complaining of cough - expectorant mixture containing 2grs. Potassium iodide per dose was prescribed.

2 hours later - choking sensation in throat - coryza very marked - face flushed - eyes puffy - respirations rapid and laboured. He recovered in about 3 hours.

A single dose of the mixture had been taken and this started the mechanism which released histamine in large quantities, giving reactions in skin, and in chest.

Mrs. S., aet 30. 1. para. ?Allergic epilepsy.

8 a.m. husband stated she had a "kind of fit" - frothed a little - tongue not bitten - one previous attack at 15 years - when menstruation began.

When seen at 8-30. - just recovering - no recollection of attack - face very flushed - respiration 42 p.m. - P.R. 120, Temp. 98 8, B.P. $\frac{90}{30}$ - incontinence of urine during "fit"

Stroke reaction-well marked flare and rapidly developed wheal - First specimen of urine after attack gave a strongly positive bromine water reaction.

Next day - felt better. Pulse and respiration normal

B.P. $\frac{114}{80}$ - Stroke reactions not so marked - whealing difficult to produce - Urinary reactions negative.

Skin reactions to diagnostic proteins negative except to meats. She stated that pork usually upset her, and she avoided it although she was very fond of it. She had had pork the previous day, and had vomited once during the night. In spite of this warning, she had pork again for breakfast, and within an hour the attack came on.

The intense flushing of the skin of the face, neck and hands, the marked fall in blood pressure, the tendency to wheal on slight stimulation, the increased respiratory and pulse rates, the positive bromine water test, and the history of hypersensitivity to pork all suggest a histamine liberation as the cause of the attack.

W.H.B., aet 38, Clerk - Angioneurotic oedema.

9. 9. 30., Extensive urticaria of face, arms and legs, T. 100°, P.R. 86, R.R. 30, B.P. $\frac{105}{75}$. Rash started in groin during the night. Calcium lactate and ephredin given.

10. 9. 30, spreading over trunk - palms of hand and soles of feet very painful with rash. T. 101°, P.R.100, R.R. 36, B.P. $\frac{100}{75}$ slight cough.

11. 9. 30., Oedema of face more marked, features hardly recognisable, T. 101·6°, P.R. 120, R.R. 40, B.P. $\frac{95}{65}$, cough worse, rales over chest. Breathing was laboured and asthmatic in type. Adrenalin 10 min. injected slowly 1 minim. every 2 minutes - sudden collapse - marked pallor of face - pulse became very thin - cold sweat over head and face: recovered in about 10 minutes. Calcium lactate given in larger doses. He had every appearance of a commencing pneumonia.

13. 9. 30, Improving, rash fading, T. 99·8°, P.R. 96, R.R. 28, B.P. $\frac{104}{70}$, chest clear. Bromine water test +ve since the onset.

7. 10. 30, after a holiday - felt well - B.P. $\frac{132}{90}$. Skin reactions for foreign proteins were negative. Serum calcium 9·8: No food stuff could be found to explain the eruption, the only unusual thing was beer of which he had 2 glasses the evening previously. Stroke reaction - flare marked - whealed with 2 strokes. The reason for the collapse following adrenalin is probably that a large proportion of the serum was in the skin tissues as transudate,

and therefore the blood volume for the heart was was not increased.

He stated that he had had several attacks but none so severe as this one. He had to discontinue swimming because of urticaria. Every time he dived into water, swam a short distance, and then came out of the water, he got an extensive urticaria which passed off usually in about 20 minutes.

The notable features are:-

Extensive liberation of histamine acting locally producing dilatation of the capillaries and transudation of lymph, and acting systemically gave increased temperature, increased respiratory rate, increased pulse rate, respiratory distress and fall in the blood pressure.

His "triple response" reaction was marked and his serum calcium was nearly normal.

Summary.

The physiological and pathological actions of histamine when injected into animals and human beings have been described, and the relationship between histamine shock, anaphylaxis and hypersensitivity has been indicated.

The results have been used to show that the mechanism of a large number of symptoms can be explained on a histamine basis.

Special mention has been made of Asthma, Acute pulmonary oedema, Measles, the bronchial and intestinal disturbances associated with teething and certain cases of hypersensitivity.

The effect of the calcium content of the tissues has been shown.

In cases where a large liberation of histamine takes place, changes in the urine have been observed.

Bibliography.

Lewis: Blood Vessels of the Human Skin and their Responses 1927

Mitchell and Hamilton. The Biochemistry of the Amino Acids 1929

Price. Text book of Medicine.

Meyer and Gottlieb. Experimental Pharmacology 1926.

Neale. Archives of Disease in Childhood, 1930.

Medical Research Committee Reports

No. 25 Wound Shock and Haemorrhage.

No. 26 Traumatic Toxaemia as a Factor in Shock.

Dale. Journal of Pharmacology 1913. Vol. 4.

Collip. Journal of Biological Chemistry 1923 - 1925.

Cameron and White. Practical Biochemistry 1930.

Dale. Croonian Lecture - Lancet 1929.

Thorpe. (Biochemical Journal 1928.)
(Journal - Physiolog. 1927)

Fraser - Goulstonian Lecture - Lancet 1927.

Marrack. Clinical Interpretation of Aids to Diagnosis 1930.

Hunter. Biochemical Journals 1922.- 1925.

Palmer ans White. Journal of American Medical Assoc. 1929.

Abel and Kubota. Journal Pharm. and Exp. Therapeutics 1919.

Hanke and Koessler. Journal Biol. Chem. 1924.

Hutchinson. Lectures on Diseases of Children - 1921.

Guttman. Presse Medicale Paris 1923.

Hendriks. Biochemical Journal XXIII. 1929.