THE RESPONSES OF THE CUTANEOUS BLOOD VESSELS UNDER PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS.

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My thesis contains the work and investigations carried out by me for the purpose of finding out whether the various skin reactions given by the cutaneous blood vessels in response to stimuli, or shown by them under certain conditions, might be helpful when applied to clinical work.

Most of my information on those skin reactions has been derived in the first place from three sources:

"The Blood Vessels of the Human Skin and their Responses" by Sir T. Lewis.

"The Anatomy and Physiology of Capillaries" by Krogh.

"Chemical Factors in the control of the Circulation" by H. H. Dale in his Croonian Lectures.

The reactions comprise:

The White Reaction.

The Red Rache.

The Wheal.

Reflex Erythema, or the Flare.

The Effect of Heat and Cold
Capillary Pulsation.

All except the last are elicited by certain stimuli, and different degrees of strength of stimulus.

The first step in the investigation was to gather together all information about the anatomy of the skin vessels; then to familiarise myself with the various reactions as they occurred under physiological conditions, to ascertain the known facts as to the mechanism of those reactions, and to apply the knowledge gained to pathological conditions.

The results have perhaps been somewhat disappointing. The principal reason of this is that the reactions included under the Triple Response, that is, the red tache, flare and wheal, are the natural responses of the vessels to pathological conditions, and so do not show any great variations.

The white reaction is opposed to the triple response in that it is a sign of constriction of the small blood vessels, while the triple response denotes dilatation.

It will be seen later that the red tache is the most constant reaction of all. It is the primary local response to injury however slight. The flare and the wheal are further steps in the reaction, depending on the severity of injury. Crammer in his book "Fever, Heat Regulation, Climate and the Thyroid Adrenal Apparatus" adduces evidence to show that all the factors concerned in heat regulation of warm-blooded animals, are under control of the sympathetic system, and therefore subject to control by the functional activity of the thyroid and adrenal glands; and that in many of the fevers due to bacterial infection, there is an increased activity of those glands.

My view is, that this is the general response to injury, and that the triple response is the local response.

The body makes an attempt to strike a balance between those two reactions.

If the local reaction is excessive, and is not held in check by the general reaction, we get such conditions as Urticaria, Asthma, Hay Fever, Anaphylaxis, and perhaps Epilepsy.

That the two responses interact, is suggested by the facts that

histamine in small doses stimulates the secretion of adrenalin, and also that injections of adrenalin suppress the action of acetyl choline on the arterioles.

In most reactions of the body to injury, the local response comes first. Histamine passes into the circulation and stimulates the adrenal and the thyroid glands to activity either directly or through the sympathetic system.

The increased secretion of adrenalin causes, either directly or through the mediation of some other chemical substance, contraction of the minute vessels of the skin. The result is the conservation of heat. The thyroid secretion causes dilatation of the small arterioles, increased metabolism, and increased production of heat.

If my theories are for the moment assumed to be correct, it will be understood that frequently diseases are not so much the result of external influence, as the result of the failure of the body to maintain an equilibrium between the general and the local reactions, so necessary for successful response.

Anatomy of Cutaneous Blood-Vessels.

Both Lewis and Krogh in their description of the cutaneous blood-vessels adopt Spalteholz as their authority. Their account of Spalteholz's work on the anatomy of the cutaneous blood-vessels, is for the most part followed here.

The deepest arterial layer forms a net-work in the cutis, where it joins the fat. Here the vessels anastomose freely with each other. From this cutaneous arterial net-work, arched and branching vessels

make their way through the cutis towards the surface. These arterioles run a sinuous course where the skin is movable, and can readily adapt themselves to stretching.

About the middle outer third of the cutis, the arched vessels and their branches form another plexus, the meshes of which vary according to the situation. In the sole of the foot they are roughly 1/3rd of a square milli-metre, in the gluteal region 1 to 1.5 square milli-metres.

These measurements are important, in that change in colour on the skin surface may cover areas which can be ascribed to dilatation, or to contraction of the arched vessels.

Lewis considers that an arched arteriole may supply two, three or four of the meshes.

This second arterial plexus is called the sub-papillary plexus. From this plexus terminal arterioles run towards the skin surface, bend over at right angles and run parallel to the surface, following the papillary ridges and giving off in their course, twigs to form the arterial limb of the looped capillaries. The terminal arteries supply on an average an area of 1/7th of a square milli-metre. They supply a variable number of papillae, and do not anastomose with each other.

The arterial limb of the capillary is narrow relatively to the end of the loop and the venous limb.

The capillary loop can be well seen microscopically, by first dehydrating the skin with alcohol and then covering a small area with cedar oil. The area is viewed by reflected light. I have

used an ordinary house electric light, adjustable, with a blue tinted glass bulb, for this purpose. The blue glass cuts off the heat and the ultra-violet rays, and shows up the vessel outlines clearly.
The low power of the microscope is used.
The number of capillaries varies in different regions.
Wetzel and Zotterman estimate the number of capillaries in different parts, and give an average per square milli-metre of 64 in the dorsum of the hand, 46 in the fore-arm, 16 in the cheek and 20 in the pale circumoral area.
It may seem strange that the pale circumoral area should contain more capillary loops than the cheeks which have normally brilliant colouring. It can be shown that the capillaries themselves play little part in skin colouring. This depends for the most part on the venules, and the depth of colour on the state of their tone. The more dilated, or the greater the diameter, the greater is the depth of colour. In the cheeks the capillaries, and more especially the venules, have a larger size than in most other regions of the skin surface.
That the skin colour depends upon the venules, can be shown by viewing the skin surface microscopically by reflected light, as before described.
The venous plexus, to which the venous limb of the capillaries drains, can be well seen by this method. If a glass slide is now taken and pressure made on the skin, as pallor develops the venules are seen to be obliterated. Further pressure obliterates the capillaries, yet pallor does not perceptibly increase.

The venous end of the capillary loop unites with others to form the collecting venules. These enter the first venous plexus, the main lines of which run along the skin ridges with the terminal arterioles, but unlike the arterioles, send off right-angled branches to join with other branches.

This first venous plexus lies immediately beneath the basis of the papillae.

Just below is another venous plexus, and between the two there is very free communication.

The two together form the sub-papillary venous plexus. This plexus lies just superficial to the sub-papillary arterial plexus.

Below the sub-papillary arterial plexus is the third venous plexus, and deeper still is the fourth venous plexus, about the level of the cutaneous arterial plexus at the junction of the deepest part of the corium with the fat.

Valves and full muscular coat first appear in the sub-cuticular veins.

There are occasional direct communications between the terminal arteries and collecting venules and even veins of the sub-papillary plexus.

Of great interest are the deeper arterio-venous communications described by Hoyer, called derivatory channels and noted by him to occur in situations where an increased supply of blood might be required to raise the temperature of parts exposed to cold, as the tips of fingers, toes, and ears.

As these investigations deal chiefly with the smallest arterioles,

capillaries and venules, the present state of knowledge of those vessels will be given in detail.

The capillaries are endothelial tubes consisting of polygonal cells, elongated and of rhomboidal shape, compared by Stohr to steel pens pointed at each end. These are cemented together by cement substance. They have an oval nucleus projecting somewhat on both the external and the internal surfaces. That the capillaries have an independent power of changing their diameter, is admitted by practically every authority at the present time. But the method by which this change is accomplished is still in dispute, although the researches of Vimtrup have done much to place on a substantial basis, the argument in favour of the presence of muscle cells on the walls of capillaries. Stricker was of the opinion that only the internal diameter of the capillary varied - presumably a suggestion that the lessened diameter was due to swelling of the protoplasm, the result of osmotic processes.

Rouget studied the capillaries in the hyaloid membrane of the frog's eye and found on the outside wall certain oval nuclei surrounded by protoplasm, occurring at intervals. From the protoplasm, projections encircled the capillaries like so many hoops.

Steinach and Kahn give measurements which show that the outside diameter of the capillaries is able to contract until it is one-half to one-sixth that of the dilated capillary.

Krogh has verified their observations and so disproves the osmotic and imbibition theory, which, if it produced any change at all on the outside surface, would cause an increase in diameter.

Vimtrup examined the capillaries of the mucous membrane of the tongue. He finds nuclei differing somewhat from ordinary endothelial nuclei, their conformation varying on dilated and on contracted capillaries.

On the dilated capillary the protoplasm surrounds the nucleus, and towards the periphery sends off prolongations which lie across the capillary, sometimes meeting prolongations from the other side of the protoplasm.

On following those cells from the capillaries to the arterioles and venules, it is found that they become shorter and change the direction of their length with reference to the capillary.

On the capillary the length lies parallel to the length of the vessel.

As the arterioles or venules are approached, the cells lie more and more obliquely, until on the stronger arterioles they assume the position and also the character of the spindle shaped muscle cells with elongated nuclei.

Krogh reproduces several of Vimtrup's figures showing the Rouget cells, which, although diagrammatic, are sufficiently convincing.

Vimtrup has succeeded in observing contraction and dilatation in the living capillaries of the tail of newt larva, and he notices that the contraction begins in the vicinity of the Rouget cells. He further observes folding of the capillary wall on contraction.

He states that he has been able to see cells identical with Rouget cells on the human capillaries and venules. He was however unable to make out the branching protoplasmic processes.

He has observed the Rouget cells on the venules of the sub-papillary plexus. This plexus, on account of its thin walls, is functionally a capillary plexus.

Krogh cites Heimberger as having observed the nail-fold capillaries of man. He demonstrates that each capillary loop is surrounded by a continuous lymph space traversed by a number of threads which keep the loop in position. If a colloidal dye is injected into this space it penetrates between the cells of the surrounding tissue.

Ebbecke describes an experiment on frogs, which shows the complete independence of the capillaries as far as dilatation and contraction are concerned.

He pins out the web of a foot and allows it to dry up slowly. At first the circulation is slow, the arteries narrow and many capillaries closed. During the first half-hour the arteries dilate, a new number of capillaries open up, and the current of blood becomes rapid. Afterwards the arteries contract again and become very narrow, yet the capillaries become more and more dilated in spite of the low arterial pressure.

Ebbecke points out that the variations in the colour of the skin in health, depend upon the quantity of blood in the capillaries and veins, and that the temperature of the skin depends upon the rate of the blood flow, which again depends upon the state of the arterioles - an increased flow if they are dilated, a diminished flow if contracted. From these two facts certain axioms applied to normal persons, may be stated.

If the hand is warm but pale, then the arterioles are dilated, and

the capillaries and venules contracted.

If the hand is cold but cyanosed, then the arterioles are contracted and the capillaries and venules are dilated.

If the hand is cold but red then the arterioles are contracted and the capillaries and venules are dilated, and the temperature of the blood is so low that reduction of the oxyhaemoglobin is reduced to a minimum.

If the hand is both cold and pale then the arterioles, capillaries and venules are contracted. This however is a pathological condition, the extreme type of which is Raynaud's Disease.

The nerve supply of the capillaries is still a matter of controversy.

It is recognised that fine non-medullated fibres derived from the sympathetic, accompany the capillaries. Generally there are two along each capillary and connected to each other by anastomosis. Krogh says that Busch has succeeded in staining very fine fibres which penetrate into the Rouget cells.

From the experiments of Steinach and Kahn on the frog's nictitating membrane, those of Hooker on the skin of the cat's ear after electrical stimulation of the cervical sympathetic, and of Krogh on the ear of the albino rabbit after the same type of stimulation, it is certainly proved that capillaries and venules contract from sympathetic stimulation independently of the arterioles.

For descriptive purposes Lewis adopts the following classification of the cutaneous vessels:

Strong arterioles	Main cutaneous arteries
	Cutaneous arterial network
	Arched arterioles
	Branches of the last
	Sub-papillary arterial network
Minute Vessels	Terminal arterioles
	Capillaries
	Collecting venules
	First Venous Plexus, Second Venous Plexus — Sub-papillary Venous Plexus
Deep Veins	Communicating veins
	Third Venous Plexus
	Communicating veins
	Fourth Venous Plexus
	Main Cutaneous veins

Lymphatic Vessels

In the skin there are very few lymphatics with an endothelial lining, but there are numerous spaces between the fibres of the corium and the cells of the epithelial layer.

The lymphatics begin as blind ends in the papillae of the skin. They pass down to a lymphatic plexus in the sub-papillary layer, then course obliquely through the corium with the blood vessels, and are collected into the larger lymphatics of the sub-cutaneous tissues.

The spaces devoid of endothelium are present between the fibres of

the corium, around the coils and ducts of the sweat glands, between the epidermal cells of the hair follicles and sebaceous glands, and between the prickle cells of the malpighian layer.

The White Reaction.

This reaction depends on the pallor which develops on lightly stroking the skin with a slight pulling action sufficient to cause a certain amount of stretching of the skin.

The reaction is best elicited by means of a flat ruler with smooth rounded ends, about three centi-metres broad. This is drawn lightly and smoothly across the skin.

As the ruler travels over the skin it presses out the blood from the venules and capillaries. As those are the vessels responsible for skin colour, the skin blanches. This immediately gives place to a slight flushing which subsides quickly, and in 15 to 20 seconds after the actual stroking of the skin, pallor commences and reaches its height in from 30 seconds to one minute. It lasts from three to five minutes.

Lewis says that it is readily provoked in young people.

I find that it occurs with greater frequency after seven years and diminishes in frequency after 25 years.

In two children, both about 7 years of age, a comparatively firm stroke - sufficient to produce a well-marked red tache in most people - was followed by a well-marked pallor.

When the stroke was heavier, although the red tache did come up, it disappeared quickly and was followed by pallor along the line of stroke.

Lewis points out that pressure on the skin does not produce the white reaction. He considers that tension of the skin is the probable factor. As proof of this he places two fingers on the skin an inch apart, and by stretching the skin between, he produces the white reaction when the tension is released.

I have found that in those cases which give the white reaction readily, the skin surrounding the red tache frequently also gives a bordering pallor about two to three milli-metres broad. This comes up in about the same time as the white reaction itself. It seems to disappear quicker than the white reaction.

This, on account of the complicated reaction of the red tache, is what one would expect.

It will be shown later that when the red tache has developed it tends to produce dilatation of the arterioles. This arteriolar dilatation will increase the pressure in the capillaries in and surrounding the red tache, and therefore the pallor surrounding the red tache will tend to disappear quicker than the white reaction.

Lewis draws attention to the sharpness of the definition of the white reaction, showing itself only on the area of skin actually touched by the ruler. There are no visible projections from the side of the white reaction. A pencil line run along the side of the ruler could scarcely produce a more defined margin.

In the anatomical description of the vessels the meshes of the sub-papillary plexus were described as varying from 1/3rd of a square milli-metre to about 2 square milli-metres in different parts of the skin.

Lewis calculated that the arched arterioles supply 2 to 4 of those meshes. If those arteries did take part in the white reaction, the pallor would overlap the line of stroke by some milli-metres. It was this that made Lewis consider that vessels smaller than the arched arterioles were involved in this reaction.

By means of the occlusion test he definitely proved that the reaction depended upon the minute vessels.

This test is simple and can be carried out by anyone.

A susceptible person is chosen who shows an easily elicited white reaction.

An ordinary blood-pressure armlet is taken and fixed in the usual way on the upper arm.

To avoid congestion of the veins, which might affect the clearness of the reaction, it is rapidly inflated to a pressure of 200 milli-metres Hg., or at least a pressure sufficient to completely arrest the blood supply to the limb.

When the pressure on the capillaries, arteries and veins has stabilised itself - this takes about one minute - the light stretching stroke is applied to the forearm of the occluded limb, and as a contrast, also to the forearm of the other limb. No difference can be observed in the white reaction on the two forearms.

With the circulation stopped, this can only mean that the capillaries and venules - the vessels responsible for skin colour - contract and force out the blood. It can not be due to passive contraction from a diminished supply of blood from contracted

arterioles.

Arteriolar contraction would only, as Lewis says, force more blood into the capillaries.

Carrier and Lewis have both observed the skin microscopically, both before and after stroking, and have seen the terminal arteries, capillaries and venules contract.

Lewis compares the pallor of mechanical pressure and the pallor of the white reaction in the occluded limb.

On releasing mechanical pressure the pallor disappears in a second or two, while in the area exhibiting the white reaction the pallor remains for about 5 minutes.

This can only mean that the vessels responsible for skin colour are contracted.

If the white tache is elicited on the forearm, or adrenalin punctured into the skin, it can be shown by means of the blood pressure armlet that the contracted venules and capillaries will withstand a pressure of from 70 milli-metres to 100 milli-metres Hg. Lewis has shown that the pressure in the veins below the armlet rises to the pressure indicated on the mercury column.

Grant, Lewis and Harris (Heart Vol. XIV No. 1.) have proved that the white reaction is independent of the nerve supply.

The Red Tache.

Trousseau in describing the Tache cérébrâle says, "If after exposing the patient, his skin be gently rubbed with a hard body, such as a pencil, or simply with the nail, the part touched becomes of a bright red colour which persists for a more or less prolonged period, that

in fevers other than cerebral the redness was never to be compared as regards intensity and duration with the redness produced in individuals suffering from brain fever. In the latter it spread for several centimetres beyond the part directly touched."
Trousseau in this passage is really describing two reactions - the reaction of the skin on the part touched, and the spreading reaction. These two reactions are due to different mechanisms. The one reaction Lewis describes as the red tache, the other as the flare. As these two terms aptly indicate the difference between the two reactions, the terms will be used here.
The red tache is produced by stroking the skin with a greater force than is used in bringing out the white reaction.
Any blunt instrument can be used such as the end of a pencil or pen. I, however, have continued to use the ruler employed in eliciting the white reaction. It gives a broad area for inspection and the pressure used can be easily graduated. The skin can be stroked along the same broad line as often as desired.
No matter which instrument is used, the result is the same, a red reaction exactly corresponding to the part of skin actually touched. With the ruler the margins of the broad red tache are straight lines, and stand out sharply delineated from the surrounding skin.
The reaction comes up speedier than the white reaction - in from 3 to 10 seconds. It is at first red in colour but gradually assumes a venous tinge.
The time of disappearance varies greatly.
Lewis has shown by his occlusion test that the red reaction occurs

even when the blood flow is completely stopped. From this, and from the sharply delineated character of the red tache he comes to the conclusion that it is caused by dilatation of the minute vessels of the skin, terminal arterioles, capillaries, venules and sub-papillary venous plexus. That is, chiefly by the vessels which give colour to the skin.

The fact that the red colour gives place to a venous tinge is an indication that the arterioles play little part in the first part of the response.

The current in the small vessels, coursing through a greatly increased bed, must slow down, and therefore allow a greater interchange of oxygen to the tissues, and carbon-dioxide back to the blood. This decreases the proportion of oxyhaemoglobin in the blood, and gives the venous tinge.

The reaction occurs on white scar tissue.

Here the colour is of a bright pink tint and it does not develop a venous tinge. This can only mean that the venules are either not so numerous in scar tissue, or that the diameter of the venules and veins of the sub-papillary plexus are very much less than in normal tissue. It follows from this, that there is less oxygen loss from the blood in scar tissue, and that the metabolism of this tissue is low.

Lewis has shown that the red reaction occurs on tissue deprived of its nerve supply.

I have tried for the reaction on over 200 persons and I have never failed to get a definite red tache.

In two cases - to be commented on later - even after stroking, the result was so slight as to be only just perceptible.

A reaction which is so general must of necessity have its basis in a physiological process.

In the occlusion test it is sometimes difficult to bring out the red tache clearly.

Lewis shows, if before stopping the blood flow completely, a pressure of 30 milli-metres Hg. is thrown into the armlet and soon after the occluding pressure applied, that under those conditions a greater quantity of blood is held up in the limb and the red tache is clearly seen, - the distinctness of the tache depending upon the amount of blood present in the vessels.

That the rate of blood flow is increased in the red tache Lewis proves by the following experiment.

A pressure of 70 milli-metres Hg. is thrown upon the veins of the upper arm and maintained for three minutes. At the end of this time the arm is deeply cyanosed. A firm stroke upon the skin of the forearm gives a well-marked red line contrasting with the surrounding cyanosed skin. This redness, representing arterial blood, is continued, showing that the rate of blood flow is increased.

Reflex Erythema.

Reflex erythema or the flare as Lewis has so pertinently termed it, **is a reaction** which occurs after the red tache. The time of appearance is variable, but is usually 15 to 30 seconds afterwards. It depends on the force exerted to produce the red tache, whether or not the flare will follow. A light stroke sufficient to produce

the red tache may not be of adequate strength to bring out the flare.

In some hypersensitive skins it follows even a light stroking, whilst on other skins very heavy strokes and even repeated strokes may fail to elicit the reaction.

It comes up readily in most babies.

The colour of the flare differs usually from the red tache. It is more of a bright scarlet colour and does not, like the red tache, change its tint when fully developed. The intensity of the colour diminishes somewhat from the central part to the margins.

It comes up around the red tache and extends on each side for a variable distance usually 1 to 3 centi-metres outside the borders of the tache. Lewis says that exceptionally it may extend for 10 centi-metres.

It very seldom appears without a preceding well-coloured red tache and obviously depends upon the factors that are responsible for the appearance of the latter reaction.

The flare comes up outside the area stimulated and the margins differ from the margins of the local reactions.

The margins of the local reactions have been described as definitely corresponding to the line of stroke. The margins of the flare on the other hand are irregular and crenated.

An important point is the areas covered by those crenations. They vary slightly but are usually from 2 to 4 milli-metres in diameter.

In my description of the anatomy of the cutaneous vessels taken from Spalteholz, the arched arterioles were described as supplying from

2 to 4 of the meshes of the sub-papillary plexus. The individual meshes cover an area of from 1/3rd of a square milli-metre to 2 square milli-metres, depending upon the region of the skin. The crenations of the margins will be found to cover areas very similar to the area supplied by the arched arterioles.

After a short interval, and while the red tache is still at its height, the flare commences to disappear. This occurs first at the margins and soon white speckled areas appear throughout the flare, leaving coloured islets scattered here and there. These too ultimately disappear and the flare area is left with the skin slightly paler in most cases, than it was before the reaction commenced.

In well-marked mottling of the forearm or other skin area, when the red tache is laid down by several strokes, the flare can be seen extending outwards rapidly along the dark areas of the mottled skin, obviously following the line of least resistance.

The pale areas become coloured also, but evidently these areas are flooded by the flare with difficulty.

Lewis's explanation of the mottled areas is that they depend upon variations in tone in the capillaries and venules, especially the venules.

He regards the pale areas as the central part of arteriolar territories, and the darker circumferential markings as the boundaries of those areas.

It is generally regarded that where the blood supply is good the capillaries and other minute vessels tend to contract. Where the

supply is deficient there is a tendency for the minute vessels to expand.

Krogh is of opinion that this depends upon whether oxygen is in excess of the tissue demands or is deficient.

Ultimately when the flare is fully developed the mottled areas tend to disappear but return again when the flare disappears.

By previously marking out the centres of the pale areas it can be shown that the mottled markings return exactly to the same positions.

If on repeated strokings no flare comes up, it will frequently make its appearance if the veins are previously congested by the pneumatic armlet, until the limb is cyanosed.

Under those conditions the flare shows up vividly red on a dark purple back-ground. This also is probably due to the difference in tone of the venules, resulting from the increased pressure.

It points to the dependence of the flare on the tone of the capillaries and venules.

Where the tone of the minute vessels is excessive the flare may fail to appear, where the tone of the minute vessels is slight the flare may spread widely.

That this is so, is seen in certain parts of the skin that have suffered injury previously.

If the tache is laid down on the skin near to those injured parts, it may happen that after the flare has extended for a certain distance it will jump the intervening skin, leaving it unaffected, and come up on the injured part.

It will be seen later when the mechanism of the flare is dealt with, that this reaction depends at least in part on the intactness of the nerves of the skin.

The point that I wish to draw attention to here, is that although there is no evident flare on the intervening skin, nerve impulses must pass along the unaffected skin to reach the previously injured skin that gives the flare. This is certainly in favour of the view that there is a continuous nerve plexus underneath the skin to which the stimuli from the various end organs run.

Lewis, Grant and Harris (Heart 1927, XIV, 1-17) have shown that the flare fails to appear if the sensory nerves to the part are completely degenerated.

On section of the sensory nerves the flare reaction is lost about the sixth day.

If the pneumatic armlet is applied and a pressure of 200 milli-metres Hg. thrown in, the local red reaction appears as usual although it is slower in developing and not so marked in colour, assuming a bluer tinge than in the normal condition.

Under those circumstances the flare fails altogether to develop.

The Wheal.

This like the red tache shows up along the line or area of stroke with strictly delineated margins. Later there is a certain amount of diffusion of fluid so that the margins become less sharply defined and overlap somewhat the original margins.

The wheal comes up to a greater or lesser extent in most skins, depending on the force used as a stimulus.

Several strokes with the end of a blunt instrument, like the end of a pencil, superimposed on each other usually produce a swelling of the skin. The usual red tache appears along the line of stroke, followed after the usual interval by the flare, then in 1 to 3 minutes swelling of the skin begins to appear and is at its height in 3 to 5 minutes.

It may project as much as 2 milli-metres above the skin surface. Lewis quotes Chatelain as having observed a case that whealed to a height of 6 milli-metres.

At first the wheal gives a pink colour, but this, owing to the increased pressure of fluid in the tissues gradually pressing the blood out of the capillaries and venules, becomes pale.

It is evident that fluid exudes only from the vessels directly stimulated.

In normal subjects I have usually found that a well-marked flare precedes the wheal.

The brighter and more extensive the flare the more evident the wheal.

There are however exceptions to this:

In one of my cases of urticaria factitia there was no flare although whealing developed rapidly and fully. In this case also, the red tache, on moderate stroking, was not marked and disappeared quickly.

According to Lewis the wheal appears even when the nerves are degenerated. It has already been stated that the flare is absent under those conditions. He states however that as the strength of

the stimulation is increased, the conspicuousness of these two independent phenomena will in general be found to increase hand in hand.

The relationship of the flare and the wheal he shows is in the rate of blood flow, and he makes a calculation which suggests that the rate of blood flow would require to be from 7 to 14 times the normal resting flow to produce a full wheal in 3 minutes.

Yet Lewis shows that neither increased blood flow nor dilatation of the minute blood vessels is sufficient to account for wheal formation.

If a pneumatic armlet is placed on the arm and a pressure of 60-80 milli-metres Hg. thrown on the veins, the whealing in a sensitive subject is diminished.

In this experiment the pressure on the capillaries and venules is increased, and those vessels are dilated, yet in spite of this dilatation whealing is diminished.

It is deduced from this experiment that dilatation of the minute vessels is not a necessary accompaniment of whealing.

By means of capillary glass tubes which are thrust into a wheal, and the fluid allowed to accumulate, Lewis shows that the protein content of wheal fluid closely approaches that of blood serum. It contains fibrinogen, one of the least diffusible of colloids, so it forms clots of fibrin on withdrawal.

Increasing capillary pressure can not be the cause of whealing, otherwise the protein content would not so nearly approach the blood serum content.

The only condition which could allow so much protein to escape from the blood, would be one of increased permeability.

If the forearm of a person sensitive to* whealing is stroked with sufficient force to produce a wheal and then placed in cold water 10° to 15° C. whealing is delayed. This seems to depend on the decreased blood supply.

Heating the skin in hot water (45°-47° C.) considerably diminishes the size of the wheal and may prevent it developing altogether.

Occlusion of the blood vessels by means of the pneumatic armlet prevents the wheal from developing while the pressure is maintained, but on release whealing quickly appears unless pressure has been maintained for too long a period - 5 minutes or over.

From this it follows that the increased permeability must be developing during the period of occlusion.

Lewis describes a condition of "refractoriness" to whealing, which he ascribes to the development of decreased permeability on the part of the vessels.

Among other experiments he strokes the back of a sensitive subject. During the final stage of subsidence of the wheal produced, fresh strokes are laid across the subsiding line. The fresh wheals are broken and reduced at the crossing points.

Evidence will be produced at a later stage, that diminished permeability does not result and that the condition of refractoriness is merely a seeming and not an actual condition.

Ebbecke shows that if trypan blue is injected into the general circulation, the dye appears in the wheal that is forming but not

in one that is already formed.

Trypan blue does not penetrate the normal capillaries, and that again is evidence of increased permeability.

Krogh cites Florey as having proved that like crystalloids, colloids pass directly through the cytoplasm of endothelial cells, but not through the nuclei.

Hoff and Leuwer using congo red injected intravenously in human beings, find that in inflamed tissues the dye leaves the vessels rapidly, and that an artificially produced wheal is coloured by the circulating dye, the amount of dye appearing in the wheal depending upon the power of the injected fluid to give pain and cause irritation.

The Mechanism of the Various Reactions.

The skin responses previously described, if we exclude the white reaction, are combined by Lewis under the term "Triple Response". He shows that the triple response is produced by different types of stimuli, mechanical, thermal, electrical, and chemical.

The constancy of this skin reaction to widely different forms of stimuli suggests a common factor as the direct cause of the reaction. The different stimuli that cause this reaction, injure the skin to a greater or less extent, depending upon the duration and intensity of the stimulus.

From this it is assumed that the triple response is the evidence of the skin response to injury - in effect that the triple response and inflammation are, at least in part, of a similar nature.

If this is so, it can be seen what a far-reaching effect the

the elucidation of the fundamental cause of the triple response would have on the study of disease.

It can hardly be doubted that response to injury in the deeper tissues and in the internal organs, will be found to depend on the same causative factor.

Lewis and Ebbecke have observed the red reaction on the surface of such organs as the liver and the spleen.

They however fail to detect any evidence of the flare.

When the vessels of the arm are occluded by the pneumatic armlet, and the red tache produced, it is found that the red tache lasts as long as the occlusion of the vessels is continued. Occlusion can not be continued too long without injury.

In the normal arm the duration of the red tache is extremely variable - it may be two minutes or it may be half an hour. In most people it has disappeared in ten minutes.

On the occluded arm it has been found by Lewis to last 25 minutes.

His opinion is that on stimulating the skin by mechanical or other stimuli, a chemical substance is released which acts on the minute vessels and causes dilatation of those vessels.

He explains urticaria factitia as an extreme sensitiveness of the skin to mechanical stimuli but not to other stimuli. In these cases the dilator substance is released in larger amounts than in normal persons.

An interesting experiment of his is to occlude the vessels of the forearm in a case of urticaria factitia, puncture in histamine, and at the same time produce the red tache by a stroke stimulus.

Histamine in very dilute concentration produces the triple response. A drop of the diluted solution is placed on the skin (1-3000 is usually employed, but dilutions of 1,-30,000 give a good response). A puncture is made through the drop, just sufficient to pierce the horny layer of the skin. In a short time a purple spot appears followed by a well-marked surrounding flare. The purple spot soon swells and a wheal makes its appearance.

In the occluded arm the purple spot from the histamine puncture, and the red tache from the stroke stimulus appear. In both, the margins extend slightly, due to diffusion of the released dilator substance. On release of the circulation, whealing occurs on the extended purple spot and the wider stroke tache.

In the normal person the red tache from a mechanical stimulus does not wheal on the release of the circulation; but if instead of one stroke, several strictly super-imposed strokes are applied to the skin, whealing occurs, as in the case of urticaria factitia.

Two experiments given by Lewis, which go far towards proving the presence of a dilator substance as being responsible for the skin responses, are:- The two arms of a subject are taken and in both the vessels are occluded for 11 minutes. At the end of one minute histamine is punctured into the forearm of one. In the other the histamine is punctured at the end of the tenth minute.

The circulation is released at the eleventh minute. Both arms flush up from reactive hyperaemia, but this dies away and soon the flare reaction comes up around both punctures. After an interval it subsides. It subsides in both arms practically simultaneously.

In the second experiment two histamine wheals are produced on the one forearm. One of the wheals is tightly bandaged over so as to allow part of the flare area to be seen at the side of the bandage. The flare around the unbandaged wheal dies away, whilst the flare showing at the side of the bandaged wheal persists in full intensity as long as the bandage is kept in place. When released it too fades away.

From the resemblance of the triple response produced by the varying types of stimuli, to the responses produced by histamine, it is postulated that the dilator substance produced is closely related to histamine.

Lewis, one feels, is convinced that the substance is histamine, but prefers to call it H-substance.

Histamine injected sub-cutaneously in small doses - 1 cc. of a 1-3000 solution - produces:-

Flushing of the skin of the face.

A rise in temperature.

A rise in pulse rate.

A fall in the systolic pressure.

A greater fall in diastolic pressure.

Lewis mentions that when considerable areas of skin are stroked in urticaria factitia, very similar effects are produced.

Dale writes that H. Kalk has recently published observations to demonstrate that stimulation of the skin in subjects showing dermatographism, is followed by a secretion of acid gastric juice, indicating that H-substance is absorbed rapidly and in amount

sufficient to give yet another of the histamine reactions.
From all the available facts, Lewis forms the general law, that "whenever the skin displays an acute reaction in the form of the triple response, this reaction is provoked directly by H-substance".
Histamine is the amino-acid Histidine deprived of a molecule of carbon-dioxide.
It is one of the active principles of Ergot. It stimulates the uterine muscle and has a marked depressor action on the circulation.
Ackermann has shown that certain bacteria decarboxylate histidine.
It is interesting to note that ergot also contains another active principle, tyramine derived from amino-acids during the putrifaction of animal matter. It can be formed by splitting off carbon-dioxide from tyrosine, and is said to act like adrenalin.
In certain investigations of Dale and Best on the therapentic value of liver extracts, they found two different factors; one with an action like that of choline dilating the stronger arterioles, the other with an action like that of histamine dilating the capillaries and venules. Eventually they isolated from alcoholic extracts of fresh liver, both choline and histamine. In the lung they found histamine in large quantities, while choline was relatively weak in amount.
Thorpe in the Biochemical Journal 1928, gives interesting estimates of histamine in different tissue extracts, in mille-grammes per kilo:

Lung	35 - 75
Epidermis	24
Ovary	9
Bladder	7.8
Spleen	5 - 7.5
Liver	2.5 - 6.6
Kidney	2.6 - 3.3
Muscle	1 - 1.4
Thyroid	0.5

The important point to note is that next to the lungs, epidermal cells contain the largest amount of histamine.

By using the lung tissues, Dale was also able to show by rapid freezing, that histamine either existed in the tissues during life, or was formed in the act of cellular death.

One of the difficulties that confronted Lewis in his attempt to bring into line all injuries affecting the skin, was the fact that certain types of stimuli produce a reaction which takes a considerable time to make its appearance. An example of this is ultra-violet light which, with an exposure of moderate duration, takes from 30 to 60 minutes before the reaction makes its appearance.

The reaction lasts for several days and differs in many other ways from the acute reaction.

Neither the flare nor the wheal develops unless the exposure has been of long duration.

The great difficulty was to explain the increased duration of the reaction.

Histamine on release seems in the acute reactions to be removed

quickly especially if there is a rapid blood flow.
Lewis explains the difference by supposing that the slowly acting stimuli release histamine in small quantities and therefore of low concentration, and that this release continues over a long period.
Dale comments on the pronounced tendency of histamine to enter into loose combination with colloidal substances.
He suggests that in circumstances altering the physiological condition of the cell substance, histamine might be liberated in one case free; in another, loosely combined with products of large molecular weight and low diffusibility.
Lewis shows that in ultra-violet irradiation, when the exposure has been sufficient to cause a considerable amount of irritation, lymphatic extensions appear running upwards from the irradiated area. These lymphatic extensions show a colour tint similar to that of the irradiated area, and are clearly due to histamine passing along the lymphatics, and dilating the over-lying blood vessels.
This in itself suggests that the histamine is in loose combination with molecules large enough to prevent its absorption by the capillaries and venules.
The present evidence is in favour of the liberation of histamine from cells other than those that are sensitive to its influence.
Dale suggests two reasons for its presence in such large amount in the lungs.
That it is an internal secretion from the lung tissue.
That it is caught up by the lung tissue when it has served its purpose in other tissues, and destroyed there.
He gives Best's evidence of its disappearance in sterile post mortem

autolysis as being compatible with the destruction theory.
Certain evidence seems to favour the idea that histamine is either produced in the liver, or reaches that organ from the intestines.
The other active principle that Dale found in his researches on liver extracts, choline, is a simple quaternary ammonium base, and has been known as a constituent of tissues, where it enters into the constitution of the group known as lecithins.
Acetyl choline, which is 1000 times as strong as choline, has been isolated from the tissues and physiologically identified by Dudley and Dale.
Dale was impressed by the similarity in action of acetyl choline and stimulation of the para-sympathetic system.
It is very unstable in the blood and is speedily hydrolysed to the relatively inactive choline.
In small doses it causes dilatation of the small arteries.
This action occurs not only in parts supplied by the para-sympathetic nerves, but also in the limbs where the only known dilator effect on the small arterioles is by means of the antidromic and axon reflex mechanism of the sensory nerves. This mechanism will be described in the section dealing with the mechanism of flare production.
Dale comes to the conclusion that the vaso-dilatation produced by antidromic stimulation of sensory fibres, or by the axon reflex, involves the liberation, in relation to the affected arterioles, of a substance which he considers is acetyl-choline.
Hinsey and Gasser are quoted by Dale as having found that adrenalin injected into the blood suppresses those effects of acetyl-choline.
Mention has been made in the preceding paragraph of antidromic

stimulation and the axon reflex.

It is now sufficiently proved that the flare depends upon the integrity of the peripheral part of the sensory nerves.

If these nerves are cut and allowed sufficient time to degenerate - Lewis gives about the sixth day as a sufficient interval - then the flare does not appear.

If however, the nerves are freshly cut, the flare develops quite as vividly as before section.

Woollard describes the sensory nerve endings in the periphery.

These throw off collaterals some of which end in the adventitial walls of the arterioles, others in the surrounding fat, in the Pacinian bodies, and in the skin.

He has traced one of the collaterals ending in the adventitia for about an inch.

It is thought that those collaterals are the efferent path for the axon reflex.

The afferent path comes through the skin terminals.

On applying any of the different forms of stimuli we have first the release of histamine causing dilatation of the minute vessels. The released histamine if in sufficient concentration, stimulates the sensory nerve endings in the skin. An impulse travels along the nerve until it reaches a collateral to an arteriole. It passes along the collateral until it reaches the wall of the arteriole where, according to Dale, it liberates acetyl-choline and we get dilatation of the arterioles.

Krogh considers that in the flare we have not merely active dilatation of the arterioles, but also an active dilatation of the capillaries

and venules.

He considers that the capillaries and venules can easily accommodate any excess of blood from dilated arterioles without themselves dilating, and that therefore increased pressure does not necessarily cause the flare reaction to appear.

In any case this minute vessels dilatation is entirely different from the dilatation in the red tache.

In the first place the colour is scarlet, showing that the bed of the minute vessels is not nearly so great as in the red tache.

The area of the flare is broken up in islets with areas of skin which show no change of colour, and may in certain cases even show an increased pallor.

The flare does not appear in an area blanched by adrenalin. The red tache on the contrary comes up readily.

In Herpes Zoster, Head and Campbell have shown that the ganglion on the posterior nerve root of the sensory nerves is affected by inflammatory processes.

Bayliss and Langley find that by stimulating the cut peripheral end of a sensory nerve to a limb, the skin of the limb flushes.

Lewis considers that in both the above instances the stimulus passes antidromically to the terminations of the sensory nerves in the skin and causes the usual reactions.

In Herpes Zoster where the stimulus is long continued a blister is formed instead of a wheal.

This blister formation seems to be characteristic of the slow reactions. It occurs also in prolonged exposure to ultra violet

light.

There is one observation made by Lewis which is particularly interesting in its relation to the nerve supply of the skin.

He found that on puncturing histamine into the skin at several points along a line, when a distance of 1 centi-metre or more separated the points from each other, a new area of flare appeared.

He thought at first that when the new flare area appeared a new terminal twig had been stimulated. Ultimately he came to the conclusion that the condition depended entirely on the tone of the minute vessels.

The reaction shows itself best on mottled skin.

If the puncture is laid down on a dark area of skin where the tone is weak, the flare rapidly spreads itself over this area and may even pass across a pale area and reappear on an adjoining part where the darker colour shows the tone of the minute vessels to be weak.

It has already been stated that wheal formation depends on increased permeability of the capillaries. Other factors such as rate of blood flow and dilatation of the vessels undoubtedly play a part, but wheal formation can occur readily without dilatation. This has been conclusively proved by Landis.

The experiments of Landis are given in detail by Krogh in his chapter on changes in the capillary permeability.

It can also occur without any change in the rate of blood flow,

although when the rate is not increased wheal formation takes place very slowly.

Owing to its strict limitation to the part of the skin showing the red local reaction, it is thought to depend also on the liberation of histamine.

Wheal formation seems to be not merely an exaggeration of the normal physiological process, but to be due to direct injury of the capillary cells.

The fluid is richer in colloids than ordinary lymph, due to increased permeability of the endothelial cells.

In physiological conditions the amount of fluid that passes from the capillaries to the tissues and from the tissues to the absorbing venules, depends on two factors:

The intra capillary pressure.

The osmotic pressure of the blood in the absorbing vessels.

An increase in the intra capillary pressure with a decrease in the osmotic pressure of the blood leads to an increased exudation of lymph from the vessels.

I know of no evidence that those two factors play an active part in the formation of wheals or of the blister. They will continue to function as in physiological conditions but the membrane through which the two forces operate will present less resistance to the passage of fluid and colloids, the only difference being that the presence of the increased percentage of colloids in the tissue spaces will increase the osmotic pressure there and so counterbalance the osmotic pressure of the blood.

This, as I understand it, is the mechanism of wheal formation.
In the experiments of Landis on the permeability of capillaries, previously mentioned, he found that if the blood vessels of the mesentry of a frog were irrigated with oxygen-free Ringer's solution for 3 - 4 minutes, the rate of filtration increased considerably.
If oxygen was now added, the rate of filtration gradually diminished.
Carbon dioxide in various concentrations up to half saturation has little effect either on the effective osmotic pressure of the blood, or on the rate of filtration.
That reactive hyperaemia is a reaction due to the liberation of histamine in tissues that have been starved of oxygen has been shown by Lewis.
The suggestion is, that the increased permeability on oxygen deprivation, was due to the liberation of the chemical equivalent of histamine in the frog.
That a similar process is responsible for the production of pathological oedema is probable.

It has not yet been ascertained experimentally whether the white reaction is due to direct stimulation of the Rouget cells, or to the liberation of a chemical substance which has a constrictor action on the minute vessels.
Both adrenalin and pituitrin, normal constituents of the body, have this constrictor action.

From certain experiments which will be described later, the primary action of adrenalin seems to be on the small arterioles, the capillaries and venules responding by contraction later.
Pituitrin acts at once on the capillaries and venules.
Nerve control exercises no influence on the reaction. It occurs equally on sensitive and on insensitive skin.
Reasoning from analogy, so many reactions have been shown to depend on chemical factors, that one is inclined to favour the view that the release of a chemical substance is the direct cause.
The latency of the reaction, longer than the tache reaction by several seconds, would favour this view.
The more rapid disappearance would suggest that if it is due to a chemical substance, then this substance is more diffusible than histamine.
It will be shown in a later section that the adrenalin and pituitrin reactions are both of longer duration than the histamine reaction.
It must however, be remembered that in the slowly acting histamine reactions (ultra-violet light) there may be a latency of $\frac{1}{2}$ an hour to 1 hour before the reaction shows itself, and that the reaction itself may last for some days.
Samson Wright carried out an investigation amongst students at the Middlesex Hospital to find out the significance of the white reaction. Systolic and diastolic pressure were taken as Emile Sargent in 1903 considered the reaction to be pathognomonic of adrenalin insufficiency. This of course proved not to be so. I am merely giving the figures to arrive at the percentage of cases giving the white reaction.

He found that:

27% gave a marked positive reaction.

39% gave a definite reaction.

34% failed to respond to the test.

20 persons attending either for dressings, or for comparatively trivial complaints were selected by me.

14 gave a definite reaction.

6 gave no reaction.

The two results agree fairly closely.

Capillary pulsation is another reaction that yields a considerable amount of information on the condition of the small vessels. The pulsation is frequently missed because the proper technique is not adopted.

A good method is to take an ordinary hand glass lens and press that lightly on the skin under examination. The necessary pressure varies on different skins and on different parts of the same skin, depending upon the state of tone of the capillaries and venules at the time of examination.

The slight magnification is a useful adjunct.

By careful observation in a well-marked case of capillary pulsation, it will be noticed that two types of pulsation are brought out by this method, pulsation in the capillaries and pulsation in the venules.

By carefully graduated pressure the blood can be pressed out of the venules in the central part of the area, leaving the venules still with a sufficient amount of blood at the margins. This is readily

effected by the slight convexity of the hand lens.

The central area is now of a pale pink colour while the margins are slightly lighter than the normal skin. The margins of this area are demarcated from the central area.

In the central area the pulsation takes the form of a movement rather like the disturbance created in a corn field by a slight wind, while in the darker area at the margins there is an ebb and flow. The marginal ebb and flow is infrequent in comparison to the movement on the central area. On this account observation of the central area is more important.

The flushing strictly coincides with the time of systole in the pulse, and the paling with the diastolic collapse.

The pulsation can be seen best towards the end of expiration. This can be readily confirmed on the lips.

I find that rarely at ordinary room temperature is there failure to detect pulsation in the lips towards or at the end of expiration.

Formerly when capillary pulsation was spoken of or observed in a case, aortic regurgitation was immediately thought of. Lewis has convincingly shown that the condition depends on the state of the arterioles. If these are dilated, then capillary pulsation is likely to be evident provided the tone of the capillaries and venules is adjusted by the necessary pressure. I have found that where the tone of the capillaries and venules is excessive, capillary pulsation is not likely to appear.

Lewis gives a series of cases of aortic regurgitation and compares the pulse pressure with the vividness and the extent of distribution

of the pulsation.

He finds that with only one exception the increase in the pulse pressure shows an increase in the vividness and extent of the reaction, so that increased pulse pressure is at least a contributing factor.

That it is not a main factor is shown by the following selected cases.

\+ signifies present.

\+ + signifies marked.

\+ + + signifies very marked.

Case	Disease	Blood Pressure		Pulse Pressure	Capillary Pulsation
		Systolic	Diastolic		
1	Aortic Regurgitation	135	75	60	Fingers +
2	Rheumatoid Arthritis	125	80	45	Fingers, Forehead, Thenar, Hypothena emminences + + +
3	Cholecystitis	145	95	50	Fingers and Lips +
4	86 years Healthy	170	100	70	Thenar, Hypothenar emminences and Fingers + +
5	Asthma	125	85	40	Thenar, Hypothenar emminences Fingers + +
6	Exophthalmic Goitre	140	95	45	Thenar, Hypothenar emminences, Fingers, Forehead + + +
7	Exophthalmic Goitre	115	85	30	Thenar, Hypothenar emminences, Fingers Forehead + + +
8	Epilepsy	130	80	50	Thenar, Hypothenar emminences, Fingers + +
9	Thrombosis of Retinal Veins, Mitral Regurgitation	200	145	75	Fingers +
10	Aortic Regurgitation with Mitral Regurgitation	130	60	70	Forehead + Fingers Nil.

Lewis shows by placing the hand in very hot water and leaving a finger free, that dilatation of the larger arteries produced by the hot water does not cause capillary pulsation.

On a very cold day the fingers frequently present a very pink tint. This can be shown to be due to dilatation of the capillaries and venules with contraction of the arterioles.

Under these conditions I have never been able to find capillary pulsation, even in cases showing vivid and extensive pulsation at room temperature.

Capillary pulsation is therefore not due to dilatation of the larger arteries, or of the capillaries and venules.

The localised mechanism of the reaction is well brought out by concentrating the light from the sun on an area 2 - 3 milli-metres in extent, by means of a hand lens. In a susceptible subject, well-marked pulsation is visible in the warmed area.

The dilatation of small arterioles, like the arched arterioles, must therefore be the cause of capillary pulsation.

It is interesting to note that in the cases given by me, two cases of exophthalmic goitre and one case of rheumatoid arthritis, where I had reason to believe there was hyperthyroidism, gave the most vivid and most extensive results.

Two cases are of course of no significance in basing an opinion as to the constant presence of any one factor, but I find on looking up certain authorities (Osler's "Practice of Medicine": Price's "Practice of Medicine": McCarrison, "The Thyroid Gland:") that capillary pulsation is emphasised as one of the symptoms. I find its frequent

occurrence in a marked form in cases that I consider show signs of hyper-thyroidism.

This being so, the suggestion is that the thyroid secretion acts on the small arterioles and causes this dilatation. It would at least partly explain the effect of the thyroid on metabolism.

Lewis states that the incidence of capillary pulsation decreases with age.

I agree that this is so. From the fact that arterial degeneration increases with the age of a person this must necessarily follow, although the state of palpable arteries is not necessarily an indication of the state of the arterioles.

The point I wish to bring out is that well-marked capillary pulsation frequently occurs in old people as the following cases show:

Case.	Age.		Capillary Pulsation.
1	86 years		Fingers, Thenar and Hypothenar emminences + +
2	85 years		Lips, Fingers and Forehead +
3	72 years	Slight Aortic Regurgitation	Whole of hands + +
4	86 years		Thenar, Hypothenar emminences and Fingers + +
5	71 years		Fingers and Hypothenar emminences +
6	68 years		Fingers +
7	80 years		Forehead and Lips +

\+ Indicates degree of capillary pulsation.

Those cases, with the exception of the case with slight aortic regurgitation, were all in very good health and all were exceptionally active and alert.

For the purpose of testing the action of certain substances on the small vessels of the skin, a small drop of the substance in solution is placed on the skin and puncture made through the drop.
The puncture should penetrate sufficiently deeply to cause a slight sensation of pain, but not deeply enough to cause bleeding.
Slight bleeding, however, does not appreciably alter the reaction.
In using this method it must be recognised that the mere pricking of the skin causes a slight reaction. This takes the form of a modified triple response.
The local response is difficult to observe at first, being eclipsed by the flare unless the skin is cyanosed from congestive pressure.
Later however, when the flare and wheal have disappeared, it remains apparent and is then slightly larger than the original area.
This increase in area is due to slight diffusion of histamine.
One must recognise the extent of the response to the simple prick.
An increase in the intensity of the response may be then rightly ascribed to the effect of the substance introduced by the prick.
In my investigations I have tested the action of many substances on the skin vessels.
A great many give the triple response, differing from the prick response by a slight increase in the intensity of the reaction.
I am giving a few of the observed responses which seem to me to have a bearing on my subject.

Adrenalin.

The preparation used was that of Parke, Davis & Co.

The strength of solution was 1 - 1000.

The response comes up quickly, one minute after the prick.
It involves, as soon as it appears, the whole area of response.
There is little if any increase in extent of the area involved as the blanching deepens.
At first the area is pale pink in tint.
It gradually loses this pink tint and becomes paler.
Ultimately the pallor is intense.
From a prick puncture the area is 2 - 5 milli-metres square, or even more.
It is irregular in outline, and the area covered varies in different punctures.
The puncture point is rarely central, and is frequently close to the margin.
It disappears in from 1½ to 2 hours, and appears to die away from the periphery towards the centre.
A series of punctures laid down in a line, a puncture to every milli-metre, gives a crenated margin almost like the margin of a developed flare.

Pituitrin.

10 international units per c.c. (Parke, Davis & Co.).

The Pituitrin puncture takes much longer to mature.
It begins to appear in from 2 to 3 minutes.
It commences at the point of puncture, and gradually extends.
The point of puncture remains central.
It takes about 45 minutes to reach its maximum size.

It gradually extends from the centre in a circular form.
The margin of the circle is distinct, and is strictly demarcated from the surrounding skin.
The area of the fully developed response is never so great as in that of adrenalin.
It is still perceptible as a white circle at the end of 4 hours.
It dies away from the centre towards the periphery.
After the reactions in both pituitrin and adrenalin punctures have subsided, a red circle develops at the site of the puncture.
This is the local reaction to injury.
If now the puncture spot is re-punctured with adrenalin or pituitrin, the blanching comes up outside the red circle, but leaves the red circle uninfluenced.
These experiments seem to me to justify the conclusion that the effect of adrenalin is primarily on the small arterioles, and that the capillaries and venules are involved at a later stage.
That the capillaries are directly involved in the reaction has been conclusively proved by Carrier and Heimberger.
They introduced a minute quantity of adrenalin into the skin in the neighbourhood of a single capillary, and observed an independent contraction of the loop.
The action of pituitrin seems to involve the capillaries and venules from the commencement of the reaction.
The speedy action and rapid disappearance of the adrenalin response compared to the pituitrin response, is a further point.
The re-puncture experiment proves that adrenalin has no power to

obliterate the dilatation of the minute blood vessels produced by histamine.

If adrenalin is punctured into the flexor surface of the forearm, into the palm of the hand - preferably the inner side where the colour is marked - and also into the finger tip, it will be observed that the forearm puncture blanches pronouncedly, in the palm the paling is just perceptible, whilst in the finger tip the colour change is almost absent.

In the above experiment, I am describing the effect on hands which are exposed to the weather. The same failure to blanch is seen in wounds of the skin which have healed, but which still show the venous colour of dilated venules.

Tyramine, another vaso-constrictor substance produces a very modified change in skin colour compared to either pituitrin or adrenalin.

It takes about 15 minutes to come up and the paling of the skin is never intense even in solutions of 1 - 100.

Histamine.

The preparation used was Ergamine Phosphatis Acidi (Burroughs, Welcome & Co.).

Histamine, in dilutions of 1 - 3000, produces an intense triple response - the local reaction obscured somewhat by the flare, the flare, of bright scarlet tint, and the wheal.

Histamine punctured into the three regions, the skin of the forearm,

the palm of the hand, and the finger tips, in hands exposed to the weather, gives a reaction which corresponds in its diminished intensity from the forearm to the finger tips, to the adrenalin response.

This shows that dilated vessels are relatively insensitive to either dilator or constrictor substances.

A mixture of the two solutions, adrenalin 1 - 1000, and histamine 1 - 3000, gives the following reaction.

There is a pallor of the skin from the adrenalin. This soon disappears and the usual histamine reaction follows.

Whealing however, is less.

When the histamine reaction has disappeared, the adrenalin pallor comes up again, and lasts for a short time. So that during the period of the histamine reaction, the adrenalin lies latent in the skin ready to produce its effect as soon as the histamine disappears.

Pituitrin introduced with the same strength of histamine has a somewhat similar effect, but owing to the longer latent period of the pituitrin reaction, the histamine response comes first.

Pituitrin seems to modify the wheal reaction more than adrenalin.

The Pituitrin effect also appears when the histamine wheal subsides.

The importance of these reactions lies in the fact that histamine, even in the greater dilution, is the all-powerful factor in the reactions.

The other substances have to stand aside until histamine has exhausted its strength.

Iron perchloride in dilution of 1 - 200 gives a wheal of large

size and there is very little local redness. The wheal lasts for several hours.

From this it would appear that Iron salts increase the permeability of the small vessels.

In the report of the Medical Research Committee on Wound Shock and Haemorrhage, Lorain Smith is stated to have found that the blood volume in Chlorosis may be doubled, showing greatly decreased permeability of the vessels.

The effect of Heat and Cold on the cutaneous blood vessels:

Lewis finds that the skin temperature in parts that are clad, varies from 30° c. to 34° c. when the temperature of the room is from 18° c. to 20° c.

This may be taken as the neutral skin temperature when there is no feeling of either hot or cold.

A skin temperature slightly below 30° c. feels cold, and a temperature just above 34° c. feels warm.

Lewis shows by inserting a thermo-electric junction into the skin, that when the arm is inserted into a water bath of varying temperature, the subcutaneous temperature may differ from the bath temperature by many degrees.

At 30° c. there is very little difference, but the more the temperature of the bath is raised or lowered, the greater the difference between the two.

At 41° c. the difference is 2° c., the subcutaneous temperature being 39° c.

At 11° c. the subcutaneous temperature is 19° c.

If two basins of water are taken with water at a temperature of 5° c. in one, and water at 45° c. in the other, and a hand is placed in each and kept there for a short time, it will be found that the colour tint in each shows practically no difference.
It will also be found that the redness produced extends just up to the water line.
This occurs when the vessels are occluded in the upper arm.
It also occurs, according to Lewis, in skin deprived of its nerves.
Applying the occlusion test, Lewis proves that the heat reaction is due to the release of histamine but that the dilatation of the vessels from cold, is a direct reaction and depends on a loss of tone of the minute vessels, really a dilatation from paralysis.
Local reddening due to heat begins to appear about 36° c.
Local reddening due to cold begins at about 10° c.
From 20° c. - 25° c. there is a tendency for the skin to become slightly cyanosed.
Lewis mentions that, according to Goldschmidt and Light, the oxygen saturation of the venous blood is generally lowest at a bath temperature of 24° c. At 34° c. the oxygen content of venous blood is normal, while over 40° c. it has almost an arterial value.
As the bath temperature is lowered from 17° c. to 6° c., the oxygen content is raised.
Brown and Hill's dissociation curves show that the blood in the minute vessels give up little oxygen to the tissues below 10° c.

That the main arteries dilate reflexly in response to heat, and contract in response to cold, can be shown by observing the reaction

of the superficial temporal artery to hot and cold water applied to the scalp, not necessarily in proximity to the artery.

That the same dilatation and contraction occur in the veins can be shown by measurement of the veins, before and after heating and cooling.

If the hand of an out-door worker is examined when the atmospheric temperature is 5° c., or slightly below, it will probably be found that the fingers in the whole of their length show a well-marked pink tint; the back of the hand will be cyanosed, and the forearm will show a pale red colour.

The lips are very sensitive to change of temperature and by lightly touching with them, the parts mentioned, they will give a good indication of the temperature variation.

The forearm will be found to be slightly warm, the back of the hand cold, and the fingers very cold.

The temperature depends on the rate of blood flow, and that chiefly on the state of the arterioles, whether dilated or contracted.

The state of the capillaries and venules will also have an effect.

If these are dilated, and the arterioles contracted, the current will be very slow, and the heat loss excessive.

If the temperature of the skin is below 10° c., the oxygen exchange will be very slight, and the blood will be rich in oxyhaemoglobin.

The skin colour under those circumstances will be of a vivid pinky-red colour.

This accounts for the pink fingers.

In the back of the hand there is a rich blood supply, as shown by the increased temperature.

The capillaries and venules are dilated and present a large surface for oxygen exchange.

At the increased temperature this occurs rapidly, and we get a venous blood deficient in oxygen.

Here the rate of blood flow does not keep pace with the oxygen exchange.

In the forearm, the slight warmth indicates a rapid blood flow, and moderate dilatation of the arterioles. This prevents the capillaries and venules being affected by the cold.

These have moderate tone as shown by the paling.

Here the state of blood flow is at a higher level than the rate of oxygen exchange.

If a pressure of 70 milli-metres of Hg. is thrown on the upper arm in the usual way, then on testing the colour tint of the forearm and hand, it is found that cyanosis begins about 15^{o} c., and is progressive until temperature up to 40^{o} c. is reached, when redness begins to appear.

There is great variation in the colour response of individuals to atmospheric temperature.

The following list gives the colour and temperature of the hands, roughly judged by the warmed finger tips in 20 cases.

The open-air temperature was about 2^{o} c.

Each case was seen within a few minutes of entering my Surgery.

Age 21 years.	Red with venous tint.	Slightly warm.
14 years.	" " " "	" "
10 years.	" " " "	Slightly cold.
43 years.	Venous tint, pink in places.	Cold.
54 years.	Pale red.	Warm.
28 years.	" "	"
26 years.	Pale.	"
53 years.	Pale-venous tint.	Slightly cold.
9 years.	Pale.	Neutral.
59 years.	Pale-venous tint.	Warm.
33 years.	Pale.	"
25 years.	Pale-pink in parts.	Slightly cold.
50 years.	Pale-red in parts.	Warm.
49 years.	Pale.	Slightly warm.
36 years.	Pale-pink in parts.	Slightly cold.
15 years.	Pale.	Warm.
22 years.	Pale-red in parts.	"
25 years.	Pale.	Neutral.
50 years.	Fingers pink. Back of hand venous tint.	Cold especially in fingers.
10 years.	Venous tint.	Cold.

The pale hand is generally warm unless it is associated with a pink tint.

The pale-red hand is warm.

Pink fingers are very cold.

The venous tint may be associated with either slight cold or slight

warmth.

The pink colour from cold appears more readily in some persons than in others.

As this occurs under similar conditions of atmospheric temperature, the early appearance of the pink colour must depend upon increased contractibility of the arterioles from the stimulus of cold.

I find that the persons who develop the pink colour readily, are the persons who develop chilblains during the winter months.

If the hand is held in very cold water for as long as possible, and a blood count taken, it will be found that the count gives a greater number of red corpuscles than a count given from a hand which has been held in hot water for a similar period.

An actual count made under those conditions was as follows:

Very Cold Water.	5 minutes immersion of fingers.	Red Corpuscles 6,192,000 per c.m.m.
Very Hot Water.	5 minutes immersion of fingers.	Red Corpuscles 4,864,000 per c.m.m.

The external appearance of the fingers after prolonged immersion in hot water, shows corrugations of the skin.

After immersion in cold water the fingers appear swollen.

In the cold water the capillaries and venules dilate, the arterioles contract.

Ultimately there is increased permeability of the capillaries with increased transudation of lymph. The fingers are swollen, and the concentration of red blood corpuscles is increased.

In hot water the arterioles dilate, the capillaries and venules dilate, the blood flow in the vessels is greatly increased, and any excess of lymph in the tissues is rapidly removed.

Leonard Hill in an article on "Humidity and Catarrh", says that cold constricts not only the cutaneous blood vessels but also those of the respiratory mucous membrane. Mudd is stated by him to have observed that local chilling of the nude body by a fan, produces vaso-constriction and consequent fall of temperature in the mucous membranes of the palate, tonsils, pharynx and nose.

I have frequently observed that a morning cold bath has the same effects.

Wakening with a congested nasal mucous membrane and headache from sinusitis, I have found that after a cold bath the headache disappears and the nasal passages become free.

Neither of those actions are direct actions on the nasal mucous membrane, but are reflex.

From the researches of Crammer on the effects of cold on the adrenal and thyroid glands, it is shown that these glands are stimulated to activity.

If we accept this, then concurrently with the increased adrenal secretion, there is contraction of the cutaneous capillaries and venules, and the probability is great, that the gland is involved in the skin response either directly or indirectly.

I have already shown that the arterioles are dilated in excessive thyroid secretion.

In my opinion the physiological response of the cutaneous surface

and the respiratory mucous membrane, to the stimulus of cold, is arteriolar dilatation and contraction of the minute vessels induced by a reflex action.

Were the response a direct one - and in pathological conditions it probably is so - the reaction would be contraction of arterioles, dilatation of capillaries and venules with excessive exudation of lymph, and bogginess of the mucous membrane - in other words an excessive local response unbalanced by the general response.

Clinically this suggests cold baths or cold sponging in the treatment of adenoids, nasal catarrh, and the recurrent bronchitis of children.

Exposure to cold air would have a similar but milder effect.

I find that I get better results from this treatment than from any other.

A gradual introduction to the cold bath is necessary.

The treatment is commenced in summer with cold sponging. Gradually the cold plunge is introduced and borne well, and if continued can be carried on throughout the winter months.

By that I do not mean to suggest that cold baths and exposure to fresh air will remove adenoids, but they will considerably ameliorate the congested condition of adenoid tissue and temporarily reduce their bulk.

Any local irritation reaching the adenoid mass will immediately cause them to swell up again so that removal is still the only permanent remedy.

Babies exposed early to fresh air conditions are, and usually

remain nose breathers.

Lewis gives it as his opinion, that there is a strong tendency in physiological conditions, for an increased tone of the capillaries and venules to develop where there is arteriolar dilatation.

This in my opinion denotes a normal activity of the thyroid and adrenal glands.

In applying the various skin reactions to pathological conditions one must have some physiological standard.

I have chosen for this purpose, ten persons most of whom I have known for a number of years. They present, so far as I am aware, no constitutional tendency to any disease, and their medical history is good.

Any illness they have had, has been of a trivial nature and never of long duration.

Six of the ten have had slight attacks of muscular rheumatism at one time or another. This condition is of frequent occurrence in my district, especially amongst the miners, and few miners escape a slight attack at some time.

Case.	Age.	White reaction.	Halo.	Tache.	Flare.	Capillary Pulsation.
1	9 years	Present	Present	Less venous than usual	Slight	Lips
2	19 "	"	None	Less venous than usual	"	"
3	17 "	"	Present	Normal	"	None
4	25 "	"	"	Less venous than usual	Nil pallor instead	None
5	30 "	"	None	Normal	Slight	Lips
6	36 "	"	Present	"	"	None
7	37 "	"	None	"	"	"
8	50 "	"	Present	"	"	Lips
9	49 "	"	None	"	"	"
10	50 "	"	"	Less venous than usual	"	None

Capillary pulsation is not noted as being present unless obvious. Most of those cases would probably show slight pulsation in the lips towards the end of expiration.

All the reactions were brought out by stroking with the ruler, and by two super-imposed strokes of moderate pressure in eliciting the tache and the flare.

The white reaction is present in all. The halo occurs in half of the cases. The flare is not marked in any and is absent in one

case.

The above results indicate that in those cases the tone of the minute vessels is good.

The obvious capillary pulsation in half the cases indicates at least moderate arteriolar dilatation.

I have previously pointed out that Krogh is of opinion that the capillaries can, without dilating, withstand any increased pressure brought to bear on them from arteriolar dilatation.

I think however, that dilatation of the arterioles usually does cause a passive increase of the diameter of the capillaries when the tone of the minute vessels is diminished.

The four cases showing a less venous tint than usual, is again an indication of good minute vessel tone, and it might also be an indication of rapid rate of blood flow.

The colour of the red tache may vary, and for descriptive purposes may be differentiated under the following heads:

1 Arterial.

2 Normal.

3 Venous.

An arterial tache may be described as one where the minute vessel tone is good and the blood flow rapid.

A normal tache comes up red and gradually develops a venous tinge.

A venous tache has a decided venous colour, and is an indication of arterial contraction and deficient minute vessel tone.

In babies and young children the three responses are readily elicited. The flare colour comes up vividly, and in contrasting it with the tache, the colour difference is slight.

To illustrate this I am giving the results in 30 children:

Case.	Age.		Flare.
1	2 years		Vivid.
2	1½ "		"
3	10 months		"
4	6 weeks		"
5	2 weeks	Marasmic child Tache only just appears.	Nil.
6	10 months		Vivid.
7	6 "		Very vivid.
8	1 year		Vivid.
9	1½ years		Very vivid.
10	2 "		Vivid.
11	8 months		"
12	2½ years		Very vivid.
13	2½ "		Scarcely perceptible.
14	8 months		Vivid.
15	6 "		Very vivid.
16	2 "		" "
17	1 month		Vivid.
18	1½ years	Congenital heart disease Blue Tache.	None.
19	2½ "	Red Tache not marked.	Slight.

Case.	Age.		Flare.
20	2 years		Slight intervening halo.
21	1½ "		Vivid.
22	8 months		"
23	6 months	Red tache not marked and disappears quickly.	No flare.
24	7 months		Vivid.
25	1½ years		"
26	1 year		"
27	7 months		"
28	1 year		"
29	7 months		"
30	9 "		"

All those reactions were brought out by a moderate pencil stroke.

In six of the cases the flare was absent or slight.

One of these was a case of marasmus, another a case of congenital heart disease.

The other four were very healthy children.

Most babies are born with deep red coloured skin with a slightly cyanosed tint - the colour in fact, of dilated minute vessels.

As the child grows older the colour is lost.

Exposure to the outside atmosphere increases the tone of the minute vessels.

This would in part explain a child's susceptibility to cold. The want of adaptation to surroundings would also explain the susceptibility

of some children to temperature extremes, compared to others.

If the red tache on the forearm and on the leg are compared, a considerable difference will be found in the colour intensity, as the following cases taken from my notes show:

Case 1: Female: Age 25 years: Lividity below knee:
On leg, red tache stands out on livid skin, but soon gives place to a distinct pallor similar to a white reaction.
On the forearm the red tache is brighter and lasts longer.

Case 2: Male, 13 years: Mottled skin above the knee.
The tache is slight, but the flare appears lighting up the dark mottled areas. Ultimately pallor develops in the flare area and obscures the darker mottling.
Below the knee the tache is difficult to see.
The forearm gives a well-marked tache.

Case 3: Male, 36 years: On the leg the red tache is just seen.
There is no flare.
On the forearm the red tache is marked and is accompanied by a flare.

Case 4: Female, 18 years: On the leg no red tache.
On the forearm, well-marked red tache.

Case 5: Male, 46 years: Case of gout.
On the leg the red tache is good.
On the forearm it is more marked and accompanied by a good flare.

Case 6: Female, 26 years: On the leg, the red tache is present but fades quickly to a white pallor.

On the forearm there is a more marked tache with a good flare.

Case 7: Female, 9 years: Chorea.

Upper leg - tache and flare marked.

Lower leg - tache just seen.

Forearm - vivid tache and flare.

Case 8: Female, 18 years: Cyanosed leg.

On the leg there is a fair tache showing up well on the cyanosed leg.

Forearm tache is brighter and more marked.

Case 9: Female, 17 years: Leg tache slight.

Forearm good.

Case 10: Female, 32 years: Varicose Veins.

Tache slight and a flare is present.

Forearm - tache more marked and a good flare.

Case 11: Female, 16 years: Several superimposed strokes bring up a slight red response on the leg.

On the usual flare area, there is pallor.

Case 12: Male, 30 years: On leg, the usual pressure gives a white reaction in place of a red tache.

On forearm, a normal tache with flare.

Case 13: Female, 22 years: On the leg, a white reaction takes the place of the red tache.

On the forearm - a normal tache and flare.

Case 14: Male, 36 years: Leg flare less marked than forearm flare.

Case 15: Male, 34 years: Sciatica.

On the leg, bright red tache with halo.

Arm - marked red tache with flare.

This patient has sciatics and has been using a stimulating liniment on the whole leg.

Case 16: Male, 54 years: Fractured leg.

This patient has been in bed for several weeks.

Leg, red tache vivid, with a pallor in flare area which lasts for about a minute followed by the flare reaction in spot areas, 2 to 3 milli-metres square.

Case 17: Male, 56 years: On leg, tache just seen and rapidly gives place to a white reaction. Even on repeated stroking the tache is not bright.

On forearm, normal tache and flare.

Case 18: Female, 36 years: Tache on leg not so marked as on forearm.

Case 19: Female, 56 years: Patient has been in bed several weeks. Tache seems quite as marked on leg as on forearm.

Case 20: Male, 65 years: Patient has been in bed for some time. The leg tache is good, but the forearm response is more marked.

The following conclusions may be drawn from those cases:

In healthy persons the tache and the flare responses are never so marked on the leg as on the forearm.

In cases which have been confined to bed for any length of time, the

forearm and leg reactions approach one another closely in intensity. A pallor may develop on the flare area, instead of the usual scarlet flush.

It might be suggested that this pallor is due to sympathetic stimulation.

The constrictor effect on both the minute vessels and the arterioles is more readily brought out on the leg than on the forearm.

If a man stands on one foot and allows the other to hang loosely so that there is complete flaccidity of the muscles, it has been calculated that the pressure amounts to 90 milli-metres Hg. in the veins of the foot. When the muscles contract, as in walking, the muscular movements empty the veins in an upward direction so that the pressure is considerably relieved.

The ready excitability of the constrictor response in the minute vessels may assist in preventing a sluggish blood flow.

It is to be noted that the pallor that frequently develops when the red tache subsides, is an active pallor with straight margins quite as distinct as those of the white reaction.

I have previously mentioned that the red tache comes up with an arterial tint in white scar tissue.

Recent scar tissue frequently gives a distinct venous colour. If a ruler is drawn along the line of scar with moderate force, a well-marked paling shows itself.

This is due to dilation of the arterioles and a more rapid flow of blood through the dilated veins of the scar tissue.

In old people it will commonly be found that the skin of the extensor surface of the forearm is thin and shrivelled, and there may be little haemorrhagic areas where the parts have come in contact with a hard object.

If a ruler is taken and the extensor surface is stroked with two superimposed strokes of moderate pressure, haemorrhage may appear in the area of the red tache. The margins of the haemorrhagic area are at first as strictly defined as in the red tache. Soon the blood diffuses into the surrounding tissue.

The injury is obviously mechanical, but the reaction shows that the haemorrhage is confined to the minute vessels, and it also shows the extreme vulnerability of these minute vessels.

In cases of high temperature at the commencement of illness, I frequently find that it is very difficult to get a pronounced red tache. When it does come up it is of a pale arterial tint and passes off quickly.

The flare is not pronounced and in many cases may fail to appear, a distinct pallor taking its place.

Whealing is very difficult to produce. Ten super-imposed strokes may fail to produce it.

As the days go on however, although the temperature continues, the red tache becomes more pronounced.

I will describe a case of pneumonia in a child of four years of age, where the reaction was observed from day to day.

For obvious reasons the wheal reaction was not included.

Age 4 years: Pneumonia: Upper left lobe affected: Temp. 105°.

1st Day: Skin dry and hot. Red tache, pale pink, comes up slowly and fades quickly.
There is no sign of flare.

2nd Day: As above.

3rd Day: Temp. 104°. Skin hot and dry. Red tache more marked and a very slight flare at the edge of the red tache.

4th & 5th Days: Very little difference.

At the end of a week when the temperature was falling by lysis, the skin was moist, the red tache and flare were well-marked, and the tache was more venous in tint.

My cases where I have observed the reaction from day to day, are limited to seven, but each of the seven cases conformed fairly closely to the above description.

In two of the cases the white reaction was especially distinct.

Crammer's experiments showing the activity of the adrenalin and the thyroid glands under conditions of high temperature, would explain the above appearances.

The rapid blood flow from arterial dilatation keeps the skin dry and warm with very little exudation of fluid from the vessels. The contraction of the minute vessels gives a feeble tache and flare.

The flare and tache were taken in 18 cases of Cardiac Disease.

Eleven were cases of myocarditis.

Seven were cases of valvular disease.

In the myocardial cases the tache was venous in four, of arterial tint in one and of normal tint in the others.

The flare was absent or very slight in eight, marked in two, and very vivid in one.

The case showing the vivid flare was one of auricular fibrillation.

In the valvular cases the tache was of normal tint in all.
The flare was vivid in five, slight in one case, and absent in the other.
The blood pressure was taken in eight of the myocardial cases. In only one was the systolic pressure below 150 milli-metres Hg. The other cases gave a systolic pressure ranging from 160 milli-metres Hg. to 190 milli-metres Hg.
In none of the cases was there any excessive pallor of the skin. In most the colour tint was good varying from a cyanosed tint to a normal tint.
Capillary pulsation was just perceptible in the finger tips in only one case, this being the case with a blood pressure below 150 milli-metres Hg. The actual blood pressure was 145 systolic and 95 diastolic.

The conclusion I draw from the above results, is that in myocardial disease the tendency is for the arterioles to be contracted.
The flare can be brought out in those cases by repeated stroking, so that thickening of the arterial coats will not account for the failure of the flare to appear on moderate stroking. The results do not to my mind warrant any further conclusions.
In eight cases of asthma, five gave a vivid and extensive flare, two a marked flare and one a slight flare.
In two cases of epilepsy the flare was marked.
Two cases of exophthalmic goitre gave a very slight flare with a well developed pallor in parts of the flare area.
These two cases of exophthalmic goitre showed capillary pulsation on thenar and hypothenar emminences, fingers, and forehead, and the pulsation was marked. The capillary pulsation indicates arteriolar

dilatation. The slight flare with areas of pallor point to increased tone of the minute vessels.

A series of cases have been examined for their susceptibility to whealing.

Here a pencil stroke is used.

I find that most people give a wheal of perceptible dimension on ten super-imposed strokes of moderate pressure.

If it comes up on five strokes it indicates increased susceptibility.

In my series of cases I have chosen for purposes of description, four degrees of whealing.

If whealing comes up with three or under three super-imposed strokes, it is described as a x x x x reaction.

Whealing with five strokes is a x x x reaction.

Seven to eight strokes is a x x reaction.

Ten strokes is a x reaction.

Case.	Disease.	Age.	Flare.	Wheal.
1	Asthma	19 years	x x x x	x x x x
2	"	48 "	x x x	x x x x
3	"	40 "	x x x	x x x
4	"	36 "	x x	x x x
5	Asthma of many years duration, associated with Emphysema	30 "	x x	Nil Marked cyanosis.
6	Asthma	40 "	x x x	x x x x
7	"	55 "	x x x	x x x x
8	"	28 "	x	x

Case.	Disease.	Age.	Flare.	Wheal.
1	Bronchitis	54 years	x	x x
2	"	36 "	x	x x x
3	"	34 "	x x	x x x
4	"	26 "	x x	x x x
5	"	30 "	x x	x x

All those cases have had several attacks of Bronchitis.

Case.	Disease.	Age.	Flare.	Wheal.
1	Pulmonary Tuberculosis	34 years	x x x	x x x
2	" "	40 "	x	Nil
3	" "	16 "	x x x	x x x
4	" "	28 "	x	x x
5	" "	42 "	x x	Nil
6	" "	43 "	x	x x x
7	" "	23 "	x	Nil
8	" "	34 "	x x x	x x x
9	" "	49 "	x	x

Case.	Disease.	Age.	Flare.	Wheal.
1	Muscular Rheumatism	54 years	x	x x
2	Subacute Rheumatism	40 "	x x x	x x x x
3	" "	13 "	x x x	x x x
4	" "	26 "	x x	x x x
5	" "	21 "	x x	x x x
6	" "	8 "	x	x x x

Case.	Disease.	Age.	Flare.	Wheal.
1	Aortic Regurgitation	26 years	x x	x
2	" "	25 "	x x	x
3	" "	39 "	x x	x x x
4	Mitral Systolic	52 "	x	x
5	Myocardial Disease	54 "	x	x
6	" "	64 "	x	x

Case.	Disease.	Age.	Flare.	Wheal.
1	Epilepsy	32 years	x x x	x x x
2	"	34 "	x x	x x x x

Case.	Disease.			
1	Exophthalmic Goitre	34 years	x	x Comes up quickly and fades away quickly.
2	" "	36 "	x	x

The conclusions from those results are:

Cases of Asthma are very susceptible to whealing and the flare is usually vivid.

The case failing to show whealing was a case of long-standing asthma associated with emphysema.

There was very evident cyanosis of the whole skin surface.

Since making the above notes I have had a patient to see me who some years ago was hardly ever free from asthma. Recently he has had very good health and except for a slight attack about a fortnight ago, he

he has been free from asthma attacks for about two years.
I have no record of his skin reaction during his attacks, but I now find a very slight flare and a just tangible wheal on ten strokes.
Formerly he was a nervous excitable man. Now his nature is more placid.
It seems to me that asthma in the nervous excitable individual may be due to exhaustion of the sympathetic system and the associated glands, and that in those people it may only be during the attacks that the local skin reactions are excessive.
I have, however, had no opportunity of testing this.
In the cases of recurrent Bronchitis whealing is pronounced.
Cases of Pulmonary Tuberculosis show no constancy in the reaction.
In Subacute Rheumatism the whealing is pronounced.
In the two cases of Epilepsy both the flare and the wheal are very marked.
In the two cases of Exophthalmic Goitre both wheal and flare are slight.
Here the wheal comes up quickly and subsides quickly.
Areas of the flare in those two cases showed well-marked pallor.

It was previously mentioned that Lewis describes a condition, which he calls refractoriness, occurring in whealing.
It will be remembered that he produces stroke whealing in a case of Urticaria factitia, and as it is subsiding, he crosses the subsiding wheal with another stroke. The new wheal is depressed where it crosses the previous wheal.
I shall describe three cases which seem to prove that it is unnecessary to assume that refractoriness, or a diminution in the permeability of

the minute vessels, is responsible for this condition.

Case 1: H.W. Age 29 years. Female:

Old injury to leg. There is extensive scarring of the left leg below the knee. A small ulcer on the scar tissue has become infected and an extensive erysipelas of the leg is now present.
There is oedema of the underlying tissue.
The patient has had several rigors and has now a temperature of 105°.
A tache stroke on the erythematous area gives in 15 seconds a pallor which soon becomes intensely white, with a slight greyish tint.
It seems to be depressed below the erythematous area, and is strictly confined to the area of ruler stroke.
It dies away in from 2 to $2\frac{1}{2}$ minutes, and as it dies away the erythematous flush again takes its place.
That it is not due to the oedematous fluid rushing into the area of stroke, is proved by pressing the blood out of the flushed skin with the finger. On releasing the pressure the flush returns at once.
On the unaffected leg a light stroke gives a very definite white reaction. The colour difference in the two reactions is definite, the deadly greyish white of the stroke area on the affected leg contrasting with the usual definite pallor of the white reaction.
Moderate stroking on the unaffected leg gives a slight red tache.

Case 2: S.F. Age 46 years. Menorrhagia.
An injection of insulin had been given the previous day. There is now a considerable swelling with a distinct scarlet flush over the swelling, and capillary pulsation can be well seen on any part of the flush.

A Pencil stroke gives a marked greyish white pallor along the line of stroke, appearing in 30 seconds and lasting about 1½ minutes.

Case 3: Baby H. Age 6 weeks.

Erythematous patches 2 - 3 centi-metres. Papules 2 - 3 milli-metres slightly raised above the surface. General flushing on abdomen. Photophobia very marked. Temperature 103°.

A Pencil stroke along a large erythematous patch, or on the general abdominal flush gives a greyish white line strictly limited to the line of stroke, and seems to be depressed below the flushed area.

It comes up quickly and passes away quickly. The exact time was unfortunately not taken in this case.

Two or three days afterwards:

The temperature is normal. The erythematous patches and papules are not nearly so distinct. The abdominal flush has gone. A Pencil stroke now gives a white line with a very faint pink tint, which is slightly raised above the erythematous patch.

One week later all the flushed patches have gone. Now a Pencil stroke gives a well-marked raised wheal. It comes up without any evident red tache, but is surrounded by a vivid flare.

Three weeks later the baby is quite well.

A Pencil stroke gives a tache with a slightly venous tint and a vivid flare. In three minutes a fully developed wheal is evident but it is not marked.

It will be noted that in all three cases there is a bright flush of the area experimented on, the bright colour suggesting arteriolar dilatation. In Case 2 capillary pulsation is very evident. Here there is no doubt

about arteriolar dilatation.

In Cases 1 and 2 the wheal seems to be depressed below the erythematous skin. In any case it certainly is not raised above the surrounding skin, as is usual in whealing.

It came up quickly and subsided quickly. It had completely subsided in two minutes.

Case 3 conformed to the two above cases at the beginning, but as the temperature and the arteriolar dilatation subsided, the wheal took longer to appear, and became raised above the surrounding skin.

When the child was quite well, the stroke resulted in the triple response coming in normal sequence and time.

I consider that in the normal histamine reaction there is a further reaction which develops probably last of all. That is, dilatation of the lymphatics, and lymphatic spaces.

In the cases given, it must be noted that the histamine response is already present. The exuded fluid is being removed rapidly by the dilated lymphatics.

By further excitation by the stroke stimulus there is increased exudation of fluid from the vessels, but that is so rapidly removed that it has no time to form a raised wheal.

The same conditions are present, to a lesser extent perhaps, in the first stroke response, in the experiment cited by Lewis. On the second stroke being laid down across the first, where they touch, the lymphatics are dilated and the fluid exuded in response to the second stimulus is rapidly removed.

I find that according to Krogh, Hoff gives a similar explanation of the refractoriness described by Lewis.

He states that in the wheal reaction the elastic properties of the skin are altered, the texture of the skin is loosened and numerous fissures are supposed to be opened up, through which the exuding fluid flows off more or less rapidly into the subcutaneous spaces.

The dilatation of the lymphatic spaces, as described by Hoff, seems to me to be the most reasonable and the simpler explanation of the failure of the wheals to mature.

In order to find out whether or not variation in the blood pressure had any influence on whealing, I took the blood pressure in the following twenty cases:

Case.	Disease.	Age.	Flare.	Wheal.	Blood Pressure Systolic.	Diastolic.
1	Asthma	19	x x x x	x x x x	115	75
2	"	36	x x	x x x	115	75
3	"	30	x x	Nil	125	80
4	"	40	x x x	x x x x	125	85
5	Pulmonary Tuberculosis	49	x	x	130	95
6	Muscular Rheumatism	54	x	x x	155	115
7	Subacute Rheumatism	40	x x x	x x x	125	75
8	Aortic Regurgitation	13	x x x	x x x	110	40
9	" "	26	x x	x	130	60
10	" "	39	x x	x x x	135	75
11	Myocarditis	54	x	x	145	95
12	Auricular Fibrillation	64	x	x	150	115
13	Exophthalmic Goitre	34	x	x	140	95
14	" "	36	x	x	115	85
15	Epilepsy	32	x x x	x x x	115	85

Case.	Disease.	Age.	Flare.	Wheal.	Blood Pressure Systolic.	Diastolic.
16	Epilepsy	34	x x	x x x x	140	95
17	Pleurisy	32	Nil	Nil	135	95
18		55	x	x	150	92
19	Neurasthenia	30	x x	x x x	130	95
20	Over-exertion	30	x x	x x x	150	95

From this there seems to be no relationship between the blood pressure and wheeling.

The following cases are selected from my notes as they seem to present certain features of interest.

Case 1: W.B. Male. Age 26 years.

Chronic parenchymatous Nephritis of at least two years duration.

Complains of severe headache and abdominal pain with sickness.

The area of cardiac dulness is increased.

Apex beat is in the sixth interspace.

The first sound is prolonged and the second sound is accentuated.

There is a systolic murmur.

The urine presents the usual characteristics.

Radial arteries hard and rigid.

Blood Pressure: Systolic 200: Diastolic 130.

Red Corpuscles count 2,204,000 per c.mm.

Retinal haemorrhage in both eyes.

A subhyaloid haemorrhage in left eye.

On the back the red tache given by heavy stroking - ruler stroke - is very faint. There are many areas of 2 - 3 milli-metres where there is no response. Even after six superimposed strokes the

tache is still faint and it vanishes quickly. There is no flare after four heavy strokes. It appears slightly after six strokes. By throwing a congestive pressure of 70 milli-metres Hg. on to the upper arm and stroking the forearm heavily with the ruler, there is just a faint arterial tache seen. A pressure of 120 milli-metres Hg. gives a slightly brighter tache.

It is noted that after the release of the congested pressure a few punctiform haemorrhages have developed.

On occluding the vessels of the upper arm for five minutes, the reactive hyperaemia on release is hardly apparent.

Capillary pulsation is not seen on fingers, hand, or forehead, but on soaking the hand in very hot water for a little time the capillary pulsation is seen in the finger-tips on withdrawal, but only for a short interval.

Ten superimposed Pencil Strokes give no whealing.

A test tube is taken quarter filled with boiling water, and the skin of the arm is touched several times with the hot test tube. A similar stimulus was applied to my own arm as a contrast.

The response in the patient is slow, there is very little flare area and the colour is of an arterial tint indicating excessive minute vessel tone.

The reactions given strongly suggests to me that the histamine supply of the tissues is diminished, at **least** relatively to constrictor substance.

The low blood count gives no indication of value in itself, but if it had been possible to obtain the total blood volume in addition, the two together might have yielded valuable information.

I refer to the action of histamine in producing increased permeability of the vessels and concentration of the red blood corpuscles.

Case 2:

This also is a case of nephritis which was admitted to hospital. The following is an extract from the hospital notes:

J.D. Male. Age 19 years. Admitted 17/7/28: Discharged 2/10/28.

Sub-acute nephritis: onset headache and slight oedema.

No history of any previous illness.

Urine - quantity considerably increased.

Specific gravity 1010.

Albumen - + + at onset, gradual decrease, complete absence on discharge.

No increase in blood pressure, or enlargement of heart.

Blood urea 70 - 47 - 34 - 42.

My tests were made in August 1929.

His condition then is as follows:

Albumen +.

Cardiac area of dulness normal.

Position of apex beat normal.

Blood pressure - Systolic 140: Diastolic 90.

Red cell count 5,392,000 red corpuscles per c.mm.

There is very definite pallor of the face and hands.

The red tache on the back is less venous than usual.

The flare is well-developed in extent but the colour is faint.

The white reaction comes up readily.

Capillary pulsation is not seen even after soaking the hand in very

warm water.

On occluding the vessels of the arm for five minutes, reactive hyperaemia on release is pronounced but passes off quickly.

In this case, judging from the skin reaction, histamine seems to be present in normal amounts.

There is excessive tone in minute vessels, as shown by the pallor without anaemia.

The failure to bring out capillary pulsation even after heating, indicates excessive tone in the arterioles and probably the minute vessels also.

Case 3: E. J. Male. Age 34 years: Urticaria factitia.

This man is susceptible also to attacks of bronchitis.

Blood pressure: Systolic 130.
Diastolic 90.

On release after occlusion reactive hyperaemia is pronounced and lasts for three minutes.

The blood count is 5,675,000 red corpuscles per c.mm.

Haemoglobin 90.

The red tache on ruler stroking is not of a vivid colour and is of an arterial tint.

Moderate stroking produces a very slight flare.

The wheal is discerned in about $1\frac{1}{2}$ minutes, and in $2\frac{1}{2}$ minutes is very pronounced.

It can be seen to form first round the hair follicles. These minute wheals extend and ultimately coalesce until the whole area is raised betwen 2 - 3 milli-metres above the skin surface.

If the area is congested beforehand the wheal is considerably modified.

On making a series of punctures through adrenalin 1 - 1000, so as to produce a large area of pallor, if now a Pencil is stroked very firmly across the pale area, the red tache appears followed by a modified wheal.

An interesting observation of the patient himself is that after a hot bath the friction of the towel causes a glossy and swollen condition of the skin surface.

The interesting features of the case are:

The marked reactive hyperaemia.

The red corpuscle count.

The arterial tint of the red tache, and the slight flare.

The pronounced wheal response.

The effect of a congestive pressure on the wheal.

The appearance of the red tache and wheal on an area where adrenalin was contracting the vessels.

Lewis states that cases of Urticaria factitia do not show an excessive histamine response to stimuli other than mechanical.

Case 4: H. F. Female. 40 years: Asthma.

This patient just lately has had several attacks during each week.

There are râles and rhonchi all over the chest.

After exertion of any kind, even a slow walk in the fresh air, she is almost sure to have an attack varying in degree according to the feeling of exhaustion.

Blood pressure: Systolic 130. Diastolic 90.

Blood count: Red corpuscles 5,365,000 per c.mm.

The red tache comes up quickly and the flare is vivid and extensive.

Whealing comes up on three super-imposed Pencil strokes.

Both the red tache and the flare are of a darker and deeper colour

than usual, and the duration of the tache is longer.
Capillary pulsation is seen on the finger pads.
The red tache comes up well on the white area after a subcutaneous injection of adrenalin.

Comments: This is a case that gives an exceedingly pronounced triple response.
It is to be noted that the asthmatic attacks on exertion come on after the effort.
This seems to point to a rapid exhaustion of the sympathetic nervous system and of the thyroid and the adrenalin glands with a resultant hyper-activity of the para-sympathetic system.
I would associate the marked local response with excitability of the para-sympathetic system.
The capillary pulsation would point to arteriolar dilatation, but I find that pronounced capillary pulsation is not present in any of my other cases of asthma.
This patient has a dread of a cold atmosphere, and the temperature of the room was high when I examined for capillary pulsation.
This might account for its presence.
There are two factors concerned in the production of arteriolar dilatation - the acetyl choline liberated by the efferent collateral in the axon reflex on stimulation of the afferent nerves by histamine; and the excessive secretion of thyroxine from hyper-activity of the thyroid gland.
The one takes part in the local reaction, the other in the general reaction to injury.
It has been stated previously that adrenalin suppresses the action of acetyl choline.

I believe that in asthma we are dealing with a condition where the individual in the endeavour to combat a harmful influence, fails because the general response to injury is weakened or is lacking, and the local response is excessive.

The asthmatic condition results not so much from an extraneous harmful influence as from the want of balance between the two reactions of the body.

The remarkable effect of very small doses of adrenalin in this case repeated three to four times a day, is due in my opinion to its deterrent effect on the too facile liberation of acetyl choline and histamine.

The blood count is high and is to my mind suggestive of a highly excitable condition of the tissues, so that they liberate histamine to certain types of stimuli just as the cases of Urticaria factitia liberate too readily an excessive quantity of histamine on mechanical stimulus.

The benefit that accrues from injections of peptone in cases of asthma is due to its histamine content.

The small doses of histamine given during the intervals between attacks, stimulate the adrenal gland to activity.

It has been pointed out by McDowall in a recent article in the Practitioner, Feb. 1930, that if peptone injections are given during an attack, the effect is to increase the bronchial spasm and turgescence of the mucous membrane.

In this case where the attacks were occurring frequently during the week, a course of peptone certainly aggravated the symptoms. Ultimately the patient refused absolutely to continue with the peptone injections.

The treatment with frequent small doses of adrenalin combined with glucose was commenced, and the patient has steadily improved. She is now able to walk a good distance without fatigue.

Case 5: C.M. Male. 52 years: Auricular fibrillation.

Area of cardiac dullness increased especially towards the right.

The slightest exertion brings on attacks of dyspnoea.

The blood pressure in this case is difficult to take. A few beats can be heard coming through at 180 milli-metres Hg.

Most beats come through at 140 milli-metres Hg.

The red blood count is 5,210,000 per c.mm.

Haemoglobin 80.

Capillary pulsation is not seen even after soaking the fingers in hot water.

These tests were carried out on the abdominal skin surface where mottling was evident.

The ruler stroke brings out a tache of venous colour.

Very soon an interesting change takes place.

Parts of the tache become of a deeper venous colour running in lines about 3 milli-metres broad across the tache.

The remaining part of the tache becomes gradually of a vivid pinky red colour, so that in the one tache we have two colours, large pink areas and narrow bands of deep venous colour.

A halo comes up round the tache 2 milli-metres broad, and in addition a less marked paling extending for 2 - 3 centi-metres outside the tache borders.

The margins of this pale area are irregular.

The pale area dies away quickly, while the halo persists.

Outside the halo some scattered pin-head spots of a bright scarlet

colour appear but these are few in number. Some may appear at a distance of 3 centi-metres from the tache border.

These few scattered scarlet spots represent the flare.

Before these spots appear, and after the pale area has disappeared, the venous lines commence to die away, and soon the whole tache area is pinky red.

The halo now extends into the tache, and very soon the tache disappears altogether, leaving a pallor in the area of stroke.

The time of disappearance is more rapid than usual.

The white reaction is very pronounced.

By previously marking out the darker parts of the abdominal mottling, I was able to assure myself that they were responsible for the venous bands running across the tache.

I interpret the results as follows:

The venous tache is due to the dilatation of all the vessels in the tache area, but the minute vessels in the dark parts of the mottled areas are very deficient in tone.

These drain the venous blood from areas where the tone is greater which are in their turn filled with oxygenated blood.

When the arterioles dilate the rapid blood flow washes the whole area of the tache with arterial blood.

The area of pallor surrounding the tache denotes contraction of the arterioles.

The marked venous colour of the tache at its commencement suggests that arteriolar contraction is present even before the stimulus is laid down.

The stimulus seems to increase the arteriolar contraction at first, and the only conclusion that seems to me to account for this

condition is stimulation of the sympathetic nerves, probably an axon reflex of the same nature as occurs in the case of sensory nerves.

When the histamine brings the sensory axon reflex into operation, the paling disappears.

The failure of the flare to appear to any appreciable extent may depend on the moderate dilatation of the arterioles being insufficient to increase the diameter of the capillaries and venules. This might be due to suppression of the acetyl choline action.

In support of this suggestion there is the failure of capillary pulsation to appear even after prolonged heating of the hand in hot water.

The pronounced white reaction and the pallor left when the red tache disappears, suggests an excessive supply of constrictor substances.

The increased pressure in the venous part of the circulation due to the cardiac condition seems to induce an arteriolar contraction and a capillary contraction where the capillary tone is good.

On this account the parts of the skin surface where the tone of the capillaries and venules is at a minimum have to bear the brunt of the increased venous pressure. These parts therefore dilate and produce increased mottling of the skin surface, and in the tache stroke are responsible for the venous lines.

Referring back to page (64) it will be noted that in the foot where there is at times a pressure of about 90 milli-metres Hg. on the veins, the responses are chiefly constrictor.

These skin responses are constant in this case.

I have notes extending over several weeks.

Case 6: A. C. Female. 56 years: Myocardial Disease.

Breathlessness on exertion.

Cardiac area of dulness increased especially towards the right.

The first sound is prolonged.

The second sound is accentuated and reduplicated.

The liver is enlarged and is felt one inch below the ribs on the right side.

Pulse 110.

There is a faint trace of albumen in the urine.

The patient is at present in bed and there is now no oedema of the legs. Before going to bed however, oedema of the ankles was present

The blood pressure is: Systolic, 220. Diastolic, 150.

Blood count: Red corpuscles 6,400,000 per c.mm.

Haemoglobin 90.

The blood count was taken twice and gave a slightly higher second count.

The colour of the red tache was not marked, and faded quickly.

Three super-imposed ruler strokes produced a moderate flare.

Whealing was pronounced on eight super-imposed Pencil strokes.

On occluding the vessels of the arm, the red tache was barely discernible.

With a congestive pressure of 120 milli-metres Hg. the tache and flare were marked.

Comments:

With the exception of whealing, the skin reactions, and the high blood pressure point to an increased supply of constrictor substance. On the contrary the high blood count and the whealing point to an excessive supply of histamine.

I decided to try the effect of a small quantity of histamine.
A tabloid containing .003 grammes of Ergamine Ac. Phosphate was injected subcutaneously. This strength is equal to 1 milligramme of histamine.
The effect was alarming. In from 30 seconds to 1 minute after the injection the patient suddenly sat up in bed gasping for breath. A vivid flush spread rapidly over the face and neck. The pulse became very rapid and in a minute or two could scarcely be felt. With difficulty she managed to gasp out that she was sure she was dying. She complained of violent beating pains in the head which seemed to cause her extreme agony. In five minutes, in spite of her condition which had not materially altered, she insisted on getting out of bed to pass urine and move the bowels. This proved to be necessary, both the bowels and the bladder acting well. These symptoms took half an hour to abate, and it was quite 45 minutes before I felt it safe to leave her.
Lewis cites Schenk as having found that doses of 6-8 milligrammes in man produce a conspicuous fall of blood pressure, respiratory distress, contraction of the stomach, and occasional collapse. One milligramme I take to be a strength which in normal persons produces slight and transient symptoms.
It is difficult to give an explanation of the extreme sensitiveness of this patient to histamine.
One explanation might meet the case.
The tissues owing to the cardiac condition are deprived of adequate oxygen supply.
Histamine is liberated in large quantity and is removed by the blood or lymphatics. In the blood it stimulates the adrenal gland and a

balance is reached between the two substances, constrictor and dilator. This balance is disturbed by the histamine injection.

It would be interesting to test the action of small doses of histamine on other myocardial cases.

Half a milligramme of histamine would be a sufficient strength to commence the experiment with.

If we accept the two propositions, that histamine is carried to the lungs for destruction there and that histamine is produced in excessive quantities in myocardial disease, then this acceptance strengthens a suggestive that cardiac asthma and acute suffocative pulmonary oedema are due to the cumulative effect of this substance overcoming the restraining influence of the sympathetic nervous system, the adrenal and the thyroid glands.

The fact that those two conditions are apt to occur in the early hours of the morning when the para-sympathetic nervous system holds power, is additional support to this suggestion.

Case 7: R. B. Male. Age 36 years.

Chronic Asthma with emphysema and marked cyanosis.

Cardiac area of dulness increased slightly to the right.

Blood pressure: Systolic 125. Diastolic 80.

Blood count: 6,539,000 per c.mm.

There is a well-marked venous tache.

The flare is + + in extent but has a darker colour than usual.

Ten super-imposed Pencil strokes give no whealing.

There is no evidence of capillary pulsation even after soaking the hand in very hot water.

The forearm and hand are inserted into a bath at a temperature of 44.5^{o} c.

The lividity of the skin is not diminished.

Insertion into a bath of 7^{o} c. does not cause the usual reddish pink colour of the skin.

In the normal case if a pressure of 70 milli-metres Hg. is thrown on the arm vessels, cyanosis of the forearm commences at 15^{o} c., and lasts until 40^{o} c. when the red reaction appears.

It appears that an increased pressure in the venous system has very little influence on the cyanosis in this case, but that it is due for the most part to defective absorption of oxygen by the lung capillaries.

Case 8: Baby H. Age 2 years: Haemophilia.

There is the usual fa mily history on the mother's side.

The death of a brother who was also a haemophiliac was due to haemorrhage.

The following skin tests were made five months ago.

The triple response is well marked, probably more so than usual.

The knees and the exposed parts of the legs above and below the knees show a marked red colouring of the skin.

Mottling of the legs is marked.

The white reaction does not show itself in any part of the body even after several careful attempts to produce it.

A fortnight ago the child developed a severe cough which from its paroxysmal nature was diagnosed as probable whooping cough.

During each attack of coughing there was severe bleeding from the nose.

The pallor and weakness of the child became alarming.

An injection was given of 8000 units of anti-diphtheretic serum in which was dissolved a 1 - 1000 adrenalin tabloid.

One slight bleeding occurred about half an hour afterwards, but there has been no recurrence of the bleeding since.

The cough continued for a week, but fortunately is now improving.

Comments:

The tone of the minute vessels seems to be defective in this case and constrictor substances diminished.

It was mentioned in the section on the red tache, that in only two cases had I had any difficulty in bringing out the red tache. One of the cases has already been described - Case 1 of this series. The other case is given below.

Case 9: A. W. 29 years: Parturition.

A large haematoma developed in the labia otherwise bleeding was not excessive.

Two days after the confinement, on two strong super-imposed ruler strokes no sign of a red tache was seen.

Three strong super-imposed strokes gave a very faint, but just discernible change in the skin colour.

That the failure of the reaction to appear on two heavy strokes was not necessarily due to loss of blood is shown by the next case.

The present case had, after the third day, a very large supply of milk in her breasts.

After a week the red tache came up in the ordinary way.

Case 10: S. W. Age 30 years.

Induced Labour: Placenta Praevia.

Patient very stout.

She lost a large quantity of blood previous to the induction of labour.

After the confinement she fainted several times.

The pulse was scarcely perceptible and very rapid.

Two days after confinement, on ruler stroking a tache developed very similar to Case 5. The blue lines however were much narrower, and the colour in the red tache was fainter.

There was quite a well-marked flare.

This patient had no milk in the breasts at any time.

Langdon Brown - "The Endocrines and the Gonads" - says that just before parturition the inhibitory effect of the corpus luteum on the pituitary gland passes off. Pituitrin passes into the blood and excites the uterus to contract.

After parturition pituitrin excites the secretion of milk.

It is possible that the pituitrin in Case 9 may have been the cause of the failure of the red tache to appear.

Case 11: J. T. Age 34 years. Female: Exophthalmic Goitre

Exophthalmos: Tachycardia: Tremor:

General flushing of skin surface:

Blood pressure: Systolic 140. Diastolic 95.

Capillary pulsation on finger pads, the whole of the palm of the hand, the forehead, and the lips.

It is pronounced and can be seen distinctly, although the pulse is 110 per minute.

The red tache has an arterial tint, and it comes up quickly.
On the back the flare is only of moderate extent and colour and there is a pallor around the flare extending into the flare area.
The tache on moderate stroking fades before the flare - a most unusual occurrence.
The wheal comes up quickly and disappears quickly.
It is marked on ten super-imposed Pencil strokes and is just tangible on five strokes.

Comments:

The tone of the minute vessels is good as shown by the arterial tache and the pallor around and in the flare area.
The rapidly fading tache is due to the speedy removal of histamine from the area.
This is effected by the rapid blood flow.
The quick wheal response and rapid subsidence is due to the same cause.
In this case we have hyper-activity of the sympathetic nervous system, and adrenal gland - as shown by the increased tone in the minute vessels - and of the thyroid gland.
The rapid local response and its speedy disappearance is due to the arteriolar dilatation.
A similar result can be got by stroking an area where the flare is already present.

Case 12: J. H. 34 years. Male.

Chronic dry Pleurisy - both sides - lasting several weeks without any change.
Temperature normal.

Blood pressure: Systolic 130. Diastolic 95.

Had chronic eczema when a child.

Even after 4 super-imposed ruler strokes the tache comes up with a very light pink colour and fades quickly, giving place to a distinct pallor.

There is no flare.

Six heavy strokes give a slight flare.

A daughter 9 years old gives an exactly similar skin response.

She suffers at present from a chronic form of eczema.

She has within the last six months had two attacks which her mother describes as fainting attacks, but from the description given me I should be inclined to think the attacks were epileptiform.

This case seems to me to be typical of a defective local response to injury. There is the chronic eczema, and the chronic pleurisy coming on without temperature and lasting for many weeks.

In the case of the daughter, if the attacks are epileptic then her skin reactions are exactly the opposite of the skin reactions in my other cases of epilepsy.

I realise that I have merely touched on the fringe of my subject. Some of the reactions, if studied exhaustively could easily have formed a subject for a thesis by themselves. My notes were made during the routine work in a busy general practice and constancy to the pursuit of information on any one part of my subject was almost impossible.

More detailed information would have been of considerable advantage and might have led to different conclusions.

For me the study has yielded a wide field of thought.

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