CLINICAL MANIFESTATIONS OF DISORDERS IN THE CIRCULATION IN THE CAPILLARIES.

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By

J. W. CRAWFORD, M.B., Ch.B.

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ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

CLINICAL MANIFESTATIONS OF DISORDERS IN THE CIRCULATION IN THE CAPILLARIES.

Within comparatively recent years considerable advances have been made in the study of the anatomy and physiology of the capillaries. The capillaries which were formerly thought to be simple endothelial tubes are now realised to be of a more complex structure than was suspected. It has been shown that the capillaries are contractile, that they are under control of the nervous system, and that they are sensitive to mechanical and chemical stimulation. They are, in fact, the principal means by which the exchange of substances between the blood and the tissue cells is regulated. The recognition of the importance of the capillaries has directed attention towards the part played by them in disease, and has led to a better understanding of the pathology of certain conditions. Cases showing evidence of disturbances in the capillary circulation are frequently met with, particularly in general practice. These clinical manifestations of capillary disorders are the subject of this paper.

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Upon the capillaries falls primarily the duty of responding to the ever-changing requirements of the cells. This necessitates a very delicate mechanism and it would be thought a priori that this must often be disturbed, and that ill-health due to disorders in the capillary circulation would be of common occurrence. It is my belief that this is so: that there are many conditions which, whatever the cause, have this in common, that the mechanism by which the symptoms are produced is a disorder of the circulation in the capillaries. When the capillaries of the skin or of an external mucous membrane are affected, the condition is readily recognisable and the process can be easily followed. When, however, the capillaries of the deeper structures are affected, the investigation is more difficult. Direct observation of the deeper capillaries in man is rarely possible during life; and as the disturbances are usually transient, and not associated with fatal diseases, the usual methods of investigation by sectioning and staining cannot be applied. Our knowledge, such as it is, of the deeper capillaries is based on observations made on lower animals, and on the reactions of the vessels of the human skin, together with some fragmentary observations of the capillaries of deeper structures in man during life.

It is a matter of some doubt how far the reactions

of the skin vessels can be applied to those of deeper structures. Especially is this so when the reactions are of an abnormal nature. Disturbances of the circulation in the capillaries of the skin are, however, often accompanied by symptoms referable to deeper structures or organs. When the same cause is responsible, and when the association is marked, it becomes probable that deeper capillaries are reacting in a similar way to those of the skin. Although these reactions in the deeper capillaries cannot be directly observed, the nature of the clinical symptoms supports this view.

In this paper particular attention will be paid to cases of urticaria because the capillary disturbance in the skin is here so definite and the associated symptoms so varied. The more chronic manifestations of capillary disturbances will also be discussed. The cases are not at all uncommon. Nor would I wish it otherwise, as disorders of the capillary circulation, far from being clinical rarities, are in reality extremely common. Any study of the abnormal must be based upon an understanding of the normal so the anatomy and physiology of the capillaries will first be described.

The anatomy and physiology of the capillaries is a subject of considerable complexity. While I do not propose/

propose to review at length the literature on the subject, the essential facts, and the methods by which these have been determined, will be discussed. The capillaries are the smallest of the blood vessels. The blood passes into them from the arterioles and is collected from them by the venules. The walls are composed of a single layer of endothelial cells of rhomboidal shape. Lying on the outer aspect of these cells there is another system of cells, the Rouget cells. These are placed at intervals along the endothelial tubes and send ramifications along them to embrace them like hoops. The staining reactions of the Rouget cells are similar to those of the cells of the muscular coat of the arterioles, and when the capillaries are traced back towards the arterioles a gradual transition between the Rouget cells and the muscle cells of the arterioles is observed. This has suggested that the Rouget cells are the muscular coat of the capillaries. Direct observation of living capillaries has established that this is so. Krogh[1] describes how Vimtrup, after stimulating the nerves to the web of a frog, observed the Rouget cells contracting, causing first indentation then constriction of the capillaries. The capillaries are, therefore, made up of two distinct sets of cells. The Rouget cells control the calibre and regulate the blood flow: the endothelial cells act as semipermeable/

semipermeable membranes and regulate the chemical exchange between the blood and the tissues. It is by alterations in calibre and changes in permeability that the capillaries respond to the requirements of the cells. It is by abnormal dilatation and permeability that capillary disturbances manifest themselves. The manner in which these changes are brought about must, therefore, be examined. The reactions of the capillaries as they are seen in the human skin will first be considered.

If a drop of highly refractive oil is placed on the skin and a strong illumination used, the superficial vessels can be studied microscopically. By this method it is seen that the colour of the skin is due to the blood in the minute vessels. The minute vessels include not only the capillaries but also the terminal arterioles and the venules. Variations in skin colour are caused by changes in the calibre of the minute vessels. If they are dilated the skin is red or blue; if they are contracted it is pale. While the colour of the skin is thus determined by the state of the minute vessels, the temperature of the skin is determined by the state of the strong arterioles. The skin temperature can be roughly estimated by the sensation imparted to the hand, and clinically, departures from the normal can usually be appreciated in this way. For accurate determinations some kind of skin thermometer is necessary

such as a thermo-electric couple by means of which small variations can be observed. The study of skin temperatures has shown that a rise in temperature is due to arteriolar dilatation with a consequent increased flow of blood, while a fall in temperature is due to arteriolar contraction with a decreased flow. When the combined findings from the study of the skin colour and the skin temperature are considered, it becomes apparent that the state of the superficial vessels can be readily determined. Five combinations of colour and temperature occur in the human skin. If the skin is red and hot both minute vessels and arterioles are dilated. If it is pale and cold both sets of vessels are contracted. If it is pale but hot the minute vessels are contracted and the arterioles are dilated. If it is red and cold the minute vessels are dilated and the arterioles are contracted. The fifth combination, that of blueness and coldness, while of common occurrence, always indicates abnormal vessels if present in a marked degree.

The superficial vessels can be easily subjected to various stimuli, and from the study of their responses much can be learned of the function of the capillaries. Mechanical stimulation by stroking the skin produces two distinct reactions according to the strength of the stroke. When a blunt instrument is drawn lightly but steadily across the skin/

skin in a suitable region, such as the forearm, a pale band appears in the area stroked in from fifteen to twenty seconds. The pallor increases to reach its maximum within a minute, then fades gradually and passes away within five minutes. This phenomenon is called the white reaction and an important conclusion has been drawn from it by the following reasoning. The skin colour is due to the amount of blood in the minute vessels. Light stroking must decrease the amount of blood in them as it causes pallor in the area stroked. Now this may be due, either to the contraction of the strong arterioles resulting in decreased inflow into the minute vessels, or to contraction of the minute vessels themselves. Lewis,[2] however, has shown that the white reaction can be obtained in a limb in which the circulation has been stopped by means of a constricting band. In this case the arterioles cannot influence the amount of blood in the minute vessels, and so it must be concluded that the white reaction is due to an active contraction of the minute vessels. In this way the independent contractility of the capillaries in man can be demonstrated. The response is not a nervous reflex as it occurs in anaesthetic skin. The reaction is due to the response of the walls of the minute vessels to the stretching produced by stroking the skin.

When the skin is firmly stroked with a bluntly pointed instrument/

instrument the red reaction appears. As in the case of the white reaction there is a latent period, but it is somewhat shorter in this case. The line of the stroke then becomes marked out by a clean-cut band of bright red colour. It fades slowly, gradually becoming bluish, and lasts for half an hour or more. The reaction is due to dilatation of the minute vessels and not to the action of the strong arterioles, as it occurs when the circulation in the arm is stopped. The nervous system plays no part as the reaction occurs in anaesthetic skin. If the stroke is very heavy, or if the skin is particularly susceptible, an additional reaction takes place. After a further fifteen to twenty seconds the skin surrounding the red line becomes flushed. This flushed area is termed "the flare" by Lewis. It is due to arteriolar dilatation. The temperature of the skin in the flare area is raised, and it does not occur when the circulation is stopped, showing that the arterioles are responsible. It is probable, however, that the capillaries also relax as it is difficult to explain the marked colour change otherwise. A flare does not appear on anaesthetised skin, and so it must be dependent on the nervous system. It occurs, however, when the nerves to the part have been cut but have not yet degenerated. It is therefore a local nervous reflex. That

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a nervous reflex can thus take place without the intervention of the spinal cord was first demonstrated by Bruce,[3] who showed that the application of mustard oil caused reddening and swelling of the conjunctival sac after the sensory nerves to the conjunctiva had been divided. When the nerves degenerated no reaction to mustard oil occurred. He applied the term "axon reflex" to this type of reflex in which no nerve cells are involved. The flare produced by heavy stroking is an "axon reflex" of the sensory nerves of the skin. Various suggestions have been advanced to explain the method by which the impulse travels from the skin to the vessels. The view now held is that the sensory nerve splits into several kinds of terminal twigs. Some branches supply the sensory organs in the skin, others supply the subcutaneous tissues and the vessel walls. The impulse passes from the skin branches, back to the axon and down the other branches to the vessels.

The red line and the flare may be the total response to firm stroking, but a third phenomenon may occur. The skin in the line of the stroke may swell and form a wheal. Whealing is readily obtained in the condition of urticaria factitia where the skin of the individual is particularly susceptible to stroking, but any skin will wheal if the stimulus is sufficiently severe. The full response to firm stroking/

stroking, comprising the local dilatation of the minute vessels, the flare and the wheal, is termed "the triple response" by Lewis. According to the strength of the stroke and the susceptibility of the individual the response may be one, two, or all three of the elements of the triple response.

The triple response follows not only stroking but any injury of the skin cells. Scratching, bruising, freezing, burning, and the application of galvanic or faradic current or of certain irritant substances all result in the triple response. The power of irritant substances to produce the response is most readily shown by placing a drop of the substance on the skin and pricking it in. By this method it has been shown that the substance which gives the most marked response is histamine. From the similarity of the response to the various forms of stimulation Lewis has come to the conclusion that the mechanism is the same in all cases. His view is, that, when the cells are injured in any way, they liberate a substance which acts on the capillaries to produce the phenomena of the triple response. This substance he calls H-substance, and he considers it to be similar to, if not actually, histamine. The substance acts first on the minute vessels causing dilatation. If the concentration of the H-substance becomes high/

high enough the sensory nerve endings are stimulated and the flare appears. The permeability of the capillaries becomes increased, fluid passes into the tissues and forms a wheal. The ready response of urticaria factitia patients is due to the fact that H-substance is more readily released from the cells by mechanical injury than in the case of a normal individual. The vessels do not respond excessively to other forms of stimuli such as pricking in histamine. The peculiarity is therefore one of the skin cells and not of the vessels.

The nature of H-substance is at present in dispute. Lewis holds that it is a normal metabolite produced by the activity of the cells, and that it acts as a local control of the circulation by producing vasodilatation in response to increased activity. When the cells are damaged, it escapes in excessive amounts into the tissues and results in the triple response. If this view is correct, the triple response is simply an exaggeration of a physiological process. The opinion is based on the reactions of the vessels when the tissues are deprived of their blood supply, and when they are subjected to moderate degrees of heat and cold. If the blood supply to a limb is cut off by placing a constricting band round it, a reactive hyperaemia follows when the blood is allowed to re-enter the/

the limb. This is due to the accumulation of metabolites which are held up in the tissues. If the deprivation of blood is continued for a long time, as can readily be done with a small area of skin, the triple response occurs. Apparently, then, the same substance, which in low concentration produces reactive hyperaemia, when more concentrated produces the triple response. Moderate degrees of heat also produce a hyperaemia, due in this case to increased metabolism of the cells which results in a free release of vasodilator metabolites. If the temperature is increased a point is reached where the concentration of H-substance again becomes high enough to produce the triple response. Cold slows down the metabolism and the skin at first becomes a little pale, soon however the paralytic influence of cold on the vessel walls predominates and dilatation with reddening of the skin results. Although the flow of blood now becomes very slow, cyanosis should not occur to any extent, as the cells require but little oxygen at low temperatures. When the temperature becomes low enough to cause damage to the cells, the triple response again appears as a result of sudden liberation of H-substance.

While these considerations appear to indicate fairly conclusively that H-substance is a normal metabolite, and responsible for vasodilatation, the question cannot yet be regarded as settled. Various other substances have formerly/

formerly been thought to be the metabolite responsible for vasodilatation. Lactic acid and carbon dioxide, both products of cell activity, cause vasodilatation when perfused through a limb. Neither of these substances, however, can produce a sufficiently powerful effect to explain the hyperaemia which is caused by increased activity. In Starling's Physiology[4] it is suggested that the substance may be acetyl-choline, as it is known powerfully to relax the arterioles. Krogh,[1] while agreeing in the main with Lewis, differs from him in several particulars. He admits that the tissue cells as a result of various stimuli liberate substances which have a dilator action on the minute blood vessels, but he does not think that the same H-substance is released in every case, and does not regard H-substance as a normal metabolite. Reactive hyperaemia and the hyperaemia produced by heating, he ascribes to oxygen lack, with the subsequent production of a vasodilator substance. Krogh finds support for his opinion, that H-substance is not the only vasodilator produced in the tissues, in the consideration of the responses to slowly acting stimuli. When the skin is exposed to ultra-violet light it becomes red, but the reaction is different in certain respects from the acute reactions which have been described. The latent period is much longer, being from thirty to sixty minutes, and no flare/

flare appears. The reaction, according to Krogh, is due not to the rapidly diffusible H-substance, but to a slowly diffusible substance of a colloid nature, which slowly accumulates in the tissues when they are acted on by ultra violet light. This substance does not stimulate the sensory nerve endings, and so no flare is produced. The alternative conception is that H-substance causes the reaction, but that it is produced very slowly, lengthening the latent period, and never reaching a sufficiently high concentration to produce the flare. Bacterial toxins fall within the group of slowly acting stimuli. When injected into the skin, as in the Dick and Schick reaction, a response is obtained which in essential particulars resembles an ultra violet light burn. When the toxins are present in the general circulation there is again a considerable latent period before the effects are observable.

The responses of the vessels which have been described have been demonstrated fully only in the skin. Bruising of the subcutaneous tissue or of the viscera, however, also causes hyperaemia and oedema, and Dale and Richards[5] have shown that similar results can be produced by painting histamine on the pancreas. It is almost certain, therefore, that the reactions of the vessels in most of the body tissues are similar to those of the skin.

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So far only the effects of local stimulation have been dealt with. The action of the nervous system on the capillaries will now be considered. Vasoconstriction is produced by impulses travelling in the fibres of the true sympathetic system. The fibres reach the vessels by two routes. The larger arteries are supplied by fibres which are continued on to them from the aortic plexus, while the smaller vessels receive non-medullated fibres from the peripheral nerves. A continuous plexus of anastomosing fibres is formed which degenerates if the sympathetic ganglia are excised. This sympathetic plexus is continued to the capillaries, and it is probable that fibres from it supply the Rouget cells. Since the time of Claude Bernard, it has been known that stimulation of the sympathetic fibres causes contraction of the arterioles; recently it has been demonstrated that capillary contraction is also caused by sympathetic stimulation. Krogh observed contraction of the capillaries in the ear of a rabbit, and in the web of a frog, when the sympathetic fibres were stimulated, and he mentions that contraction of the capillaries at the base of the nail in man has been observed when the sympathetic fibres in the adventitial coat of the humeral artery were stimulated. He is of the opinion that wherever the sympathetic fibres produce constriction of the arterioles/

arterioles, so also do they produce constriction of the capillaries. Although the sympathetic system causes constriction of the vessels, it can bring about an increase in the blood supply to any region. The arterioles elsewhere in the body can be contracted, and the heart's action stimulated to increase the general blood pressure, and the tone of the arterioles and capillaries in the area of activity relaxed to produce an increased flow to the part. The phenomenon of blushing is an example of the way in which relaxation of the tone of the vessels can occur through sympathetic action. The fact that the capillaries as well as the arterioles take part in the reaction is shown by the marked change of colour in the skin. The sympathetic, however, is essentially vasoconstrictor in function and the vasodilator fibres are of an entirely different nature.

From analogy with the innervation of other visceral muscle, it would be expected that the parasympathetic nerves would be the vasodilator nerves of the body, as they usually act in the opposite way from the true sympathetic. This is so in only a few instances. Stimulation of the chorda tympani causes vasodilatation in the submaxillary gland and stimulation of the nervi erigentes has a similar effect on the vessels in the corpora cavernosa and spongiosa. These are isolated examples, however, and on the vessels elsewhere/

elsewhere throughout the body the parasympathetic has no effect. Vasodilatation does occur as a result of stimulation of nerves, but the fibres responsible do not belong to the autonomic system but are the medullated sensory fibres of the somatic system. This was first demonstrated in 1876 by Stricker, who stimulated the cut dorsal roots of the limb plexuses and produced dilatation in the vessels of the skin. Mechanical stimulation of a mixed nerve such as the sciatic also causes dilatation of the vessels. The fibres responsible are stated by Bayliss(6) to be "anatomically indistinguishable from the ordinary sensory afferent fibres, failing to degenerate when the roots are cut between the cord and the ganglia but degenerating when the dorsal root ganglia are removed." He applied the term "antidromic" to this form of stimulation, since the impulse passes along the nerve in a direction contrary to the usual sensory impulse travelling towards the spinal cord. He held the view that the sensory nerves were genuine vasodilator nerves. His work applied to the arterioles only, but it has since been shown that the capillaries also dilate as a result of antidromic stimulation. That the dilatation of the capillaries is not simply a passive one has been demonstrated by first applying acetyl-choline which produces a maximum dilatation of the arterioles, and then stimulating the sensory nerves. A further dilatation of the capillaries takes place following/

following the stimulation, and must therefore be due to the action of the nerves on the capillaries themselves. In man the condition of herpes zoster provides a striking example of the effects of antidromic stimulation. The ganglion of the posterior root of the sensory fibres becomes acutely inflamed and impulses pass down the sensory nerve to the skin, where dilatation of the vessels occurs and herpetic lesions are produced. Irritation of the posterior roots by tumours or injury causes a similar skin condition, while if a nerve is injured in its course the circulatory disturbance is shown by the trophic lesions which so commonly develop in its area of distribution. The effect of stimulating the sensory nerve endings in the skin on the vessels, which has been already referred to when discussing the axon reflex, is again the production of vasodilatation, and completes the evidence that stimulation of the sensory nerves in any part of their course will cause dilatation of the vessels.

The sensory nerves do not act directly on the vessels. Anatomically it would be impossible for them to do so, for although a plexus of sensory nerves is present on the smaller arteries and arterioles the fibres do not penetrate the muscular coat, and are not continued on to the capillaries. The capillaries, however, actively dilate as a result of antidromic stimulation and therefore must/

must be affected indirectly by the nerves. The tissue surrounding the capillaries is supplied by numerous sensory nerve twigs and it is the action of these on the tissue cells which explains the vascular reactions. When the nerve is stimulated, a diffusible chemical substance is liberated from the tissue cells which causes dilatation of the vessels. This has been demonstrated by Lewis. He occluded the circulation in the limb of a cat and stimulated the sensory nerve. The occlusion was maintained for a period longer than the usual flushing period of the paw following antidromic stimulation. When the circulation was restored, and when the reactive hyperaemia due to the occlusion had subsided, flushing of the paw from the stimulation of the nerve was observed. This lasted for the usual length of time, and it is difficult to imagine an explanation other than that a diffusible chemical vasodilator was produced in the tissues by the stimulation of the nerve, and held there during the occlusion of the circulation. The substance formed, in the opinion of Lewis, is that same H-substance which is produced when cells are injured by local stimulation. It has been already mentioned that H-substance is regarded as a normal metabolite and the triple response as an exaggeration of a physiological process. In the same way Lewis regards antidromic stimulation of the cells as a physiological process, and the vascular/

vascular responses which occur as a result of stimulation experimentally, or by pathological processes, as an exaggeration of the normal function of the nerves. The skin cells are considered to be reservoirs of H-substance under the control of the sensory nerves. Whether the nerves regulate the escape of the dilator substance by controlling the metabolites in the cells, or by altering the perviousness of the cell walls, has not yet been decided. A very similar view of the action of the sensory nerves on the cells has been expressed by Gaskell.(7) He compares the glossy skin and trophic changes which result from injury to the sensory nerves, to the paralytic secretion and cellular atrophy which occur in the submaxillary gland when the chorda tympani is cut, and considers that the sensory nerves control the metabolism of the epithelial cells in the same way as the secretory nerves control the gland cells.

The conception of antidromic stimulation as a physiological process is of great importance, as, if it is correct, the sensory nerves must play a considerable part in the regulation of the metabolism of the cells. In this connection it is important also to remember that Mackenzie(8) emphasized the influence which the metabolism of cells in turn exerts on the nervous system. The receptive fibrils of nerves receive impulses not from environmental conditions but from other cells. Cell-activity causes discharge of energy/

energy or impulses from the cells. When the activity of the cells is increased the discharge of impulses is also increased and stimulates the nerve fibrils. As an example of this, Mackenzie instances the observation made by Ramsay that a blister on the temple will increase the dilatation of the pupil produced by atropine. The blister does not directly affect nerve endings, but stimulates the cells of the skin to increased activity, and it is this alteration in the metabolism of the cells which causes stimulation of the nerve endings. It is clear, therefore, that the nervous system is intimately concerned with cell activity. Impulses generated in the nervous system affect the metabolism of the cells, while the metabolism of the cells in turn generates impulses which stimulate the receptor endings of the nervous system.

The control of the capillaries by local influences, by the nervous system directly, and indirectly through the medium of the tissue cells, has now been discussed, and there remains only the action of the endocrines to be considered. Of these the suprarenals and the pituitary are of greatest importance. By pricking adrenalin and the extract of the posterior portion of the pituitary into the skin it can be shown that both cause constriction of the minute vessels. Experiments on animals have suggested

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that adrenalin acts chiefly on the arterioles, while the pituitary extract acts chiefly on the capillaries. Both substances are normally present in the blood stream, but their function in respect to the minute blood vessels has not yet been determined. It has been suggested that they serve either to maintain the tone of the arterioles and the capillaries, or to counteract the effect of the vasodilator metabolites when they reach the general blood stream. That the presence of vasodilator substances in the general blood stream can profoundly affect the vessels is demonstrated in the condition following extensive burning, and in surgical shock. In these conditions, there is a mass entry of H-substance formed in the injured area into the circulation and widespread capillary dilatation results. If this substance is prevented from entering the blood stream by amputation of the lacerated area, or in the case of burns by fixing it in the tissues by spraying with a solution of tannic acid, the ill-effects may sometimes be prevented. When general capillary dilatation has occurred, it cannot be controlled by the injection of adrenalin or pituitary extract, and it seems probable that if these substances do counteract the vasodilator metabolites, they do so before any action on the vessels has taken place.

The substance liberated by injury to the cells affects

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not only the calibre of the vessels but also the permeability of the vessel walls, and in the skin causes whealing if in sufficient concentration. Whealing is a form of local oedema, and to understand its production it is necessary to consider how the balance is maintained between the amount of fluid in the blood stream and in the tissue spaces. The blood in the capillaries is under a certain pressure as a result of the action of the heart. This pressure tends to force the fluid out of the capillaries. Balancing this is the osmotic pressure of the blood colloids to which the capillary wall is impermeable. This tends to draw the fluid from the tissues into the capillaries. If the pressure in the capillaries is higher than that due to the osmotic action of the blood colloids, fluid will pass into the tissues, and if not drained away quickly enough by the lymphatics, will cause oedema. This occurs in heart disease where the pressure in the capillaries is affected by the congested venous system. If the osmotic pressure of the colloids is reduced, as in nephritis, where a loss of colloids takes place via the kidney, oedema will again result. A third method by which oedema may occur is by alteration in the permeability of the capillary walls. If the walls become more permeable the osmotic pressure of the blood is virtually lowered, and the balance is again upset.

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The whealing of the triple response is due to this cause. The increase in permeability is not due to the dilatation of the vessels but to the action of the H-substance on the endothelial cells of the capillaries.

This completes the survey of the anatomy and physiology of the capillaries, and cases illustrative of capillary disturbances will now be described.

Case 1. Master McL. Aged 5.

This boy suddenly developed a severe attack of urticaria, oedema, and asthma. When examined, large wheals were present on the trunk and limbs. The face was greatly swollen and there was oedema of the legs. Respiration was difficult, and there was much wheezing. The attack gradually passed off, and within two days the boy had quite recovered. His mother attributed the illness to the fact that on the day prior to the onset he had eaten two boiled eggs. In view of the marked susceptibility of the boy, as shown on former occasions, to ingested proteins, I considered that this was the correct explanation. His previous history is of considerable interest. He was a healthy, breast-fed baby until nine months when he was weaned. After his first feed of cow's milk he developed an attack of urticaria/

urticaria, oedema, and asthma similar to that described above. Ever since, he has been unable to take even the smallest amount of milk without suffering from an attack of the same kind.

The interesting feature in this case is the repeated association of urticaria, oedema, and asthma. There can be no doubt that these symptoms have a common cause, namely susceptibility to foreign proteins. The point which I wish to consider, however, is whether the mechanism by which the symptoms are produced is the same. Urticaria differs little in pathology from the triple response produced by injury to the skin cells. The erythema and whealing are caused by capillary dilatation and increased permeability. The liberation of H-substance from the cells in this case, however, is due to the action of a foreign protein carried in the blood stream. The reaction is an allergic one, that is the cells usually require to have been sensitised to the substance by having been previously brought into contact with it. Sometimes this does not appear to be necessary, as in the case of this boy who reacted to the first feed of cow's milk. While the sensitivity of the skin cells must be held responsible for the reaction, the visible effects were produced by the resultant changes in the capillaries. The

oedema/

oedema of the face and legs in my opinion was the result of similar changes in the capillaries of the subcutaneous tissues. In discussing oedema it was stated that it may be caused by venous congestion, by loss of colloids, or by changes in the permeability of the capillaries. It is not implied that oedema cannot be caused in other ways, as for example by salt retention, but that these are the most important so far as the capillaries are concerned. In this case there was no venous congestion, and no albumin was found in the urine, so it is reasonable to assume that the oedema was caused by an increase in the permeability of the capillaries. It cannot be definitely stated that capillary dilatation also occurred, but it seems probable that it did so and that the oedema was due to a reaction of the capillaries of the subcutaneous tissues similar to that which in the skin caused urticaria. That the capillaries of the subcutaneous tissues like those of the skin may be affected by the nervous system is shown by the condition of angio-neurotic oedema which is characterised by the sudden appearance of local oedematous swellings.

Asthma, the third of the associated symptoms in this case, while due primarily to spasm of the bronchial muscles, also shows evidence of the involvement of the capillaries, in the congestion of the bronchial mucous membrane. The association between instability of the skin capillaries to

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foreign proteins and asthma is demonstrated in the skin protein tests. A protein which will precipitate asthma, when pricked into the skin, will produce an urticarial wheal. A mild degree of the same reaction would explain the congestion of the bronchial mucous membrane in asthma. There is no doubt that clinically there is a marked association between asthma and urticaria as urticaria is particularly common in asthmatic subjects.

The following case again demonstrates the association of urticaria, oedema, and asthma, and in addition shows how the injury to the skin cells may result in dermatitis.

Case 2. Mrs K. Aged 65.

For many years this patient has suffered from bronchitis and asthma. The bronchitis never really clears up, but at times improves considerably. During one of these periods of relative freedom from bronchitis, she ate a quantity of prawns and the next day had a severe attack of urticaria and the bronchitis immediately became much worse. The urticaria affected principally the skin of the forearm and lower limbs. There was great swelling of the legs from the knees downwards, particularly round the ankles and on the dorsi of the feet. The whealing subsided within

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two or three days, but the skin remained red, and by the end of the week dermatitis had developed. This varied according to the site. On the forearms it was of the papular type, on the groins moist and weeping, and on the skin between the toes of the bullous type with the formation of fluid blisters. This dermatitis took four weeks to clear up.

Most of the features of this case have already been discussed, but I wish to direct attention to the development of the dermatitis following the urticaria. From the view already given of the pathology of urticaria, it is clear how this occurred. In urticaria the essential lesion is in the skin cells, but the damage to them is rapidly recovered from. In this case the usual recovery of the normal metabolism of the skin cells did not take place and inflammation of the skin resulted.

In the next case the effect of changes in the capillaries of joints is seen.

Case 3. Mr B. Aged 32, following a slight wound, developed a mild cellulitis of the left forearm. The condition responded well to hot fomentations and incision, and by the end of a fortnight he had almost recovered. At this stage, he ate some tinned salmon and about twelve hours later urticaria appeared. Pain in the arms and in the right knee was also complained/

complained of. On examination the right knee was found to be swollen and fluid was present in the joint. There was stiffness and limitation of movement of both shoulder joints. There was no rise of the patient's temperature and his general condition was not affected. The fluid in the knee joints gradually became absorbed and had gone in four days. The stiffness of the shoulder joints passed away at the same time.

The joint conditions in this case could not have been due to an extension of infection from the arm, as the bacterial invasion of three large joints would have produced a marked systemic disturbance. Again, the onset at the same time as the appearance of the urticaria suggests a common cause. The effusion of fluid was almost certainly caused by a reaction in the capillaries of the membrane lining the joint similar to the reaction which in the case of the skin capillaries produced urticaria. The patient had often eaten tinned salmon before and had never been upset in any way by it. The salmon in this instance was eaten by other members of the household without ill-effects. The most probable explanation is that the absorption of toxins from the cellulitis affected the capillaries of the patient and rendered them unstable to the protein of the salmon. The following is a somewhat similar case. A young woman, following a minor/

minor operation, developed a little suppuration. On the first day of the next menstrual period an extensive attack of urticaria occurred. In this case the absorption of toxin rendered the capillaries unstable to the hormone causing menstruation. In cases of chronic absorption from toxic foci, the sudden liberation of a large amount of toxin into the blood stream, as for example when a septic tooth is extracted, may cause urticaria, and it is possible that much of the ill-health due to toxic foci occurs through the production of a state of chronic capillary instability.

The close association between bacterial toxins and rheumatic joint conditions has been repeatedly noted. Acute rheumatism is often preceded by a streptococcal tonsillitis, and there is now a considerable amount of evidence in favour of the view that the sudden joint effusions are an allergic reaction, due to the sensitisation of the tissues by the streptococcal toxins. Allergic reactions become manifest by changes in the capillaries, and if this view of acute rheumatism is correct, it must be included in the conditions in which the visible effects are produced by a disturbance in the normal balance of the capillaries. It must be remembered however that, as Poynton and Schlesinger (9) emphasize, an allergic element in rheumatism does not exclude a bacterial origin for the disease, since for the

production/

production of the allergic state a bacterial antigen is essential. Llewellyn[10] ascribes an even more important rôle to the vessels in the production of acute rheumatism. He describes a pre-rheumatic phase characterised by vasomotor instability, and considers this instability to predispose to rheumatic infection. The cause of the instability is attributed to "endocrine-autonomic imbalance." He also emphasizes the importance of vasomotor instability in rheumatoid arthritis. In the skin, this is shown by the glossiness and poor circulation, while the wasting of the muscles and joint changes are thought to be due at least in part to capillary spasm. I do not propose to discuss the evidence in favour of this view but to refer to a simpler example of the way in which circulatory disturbance may cause arthritis. Occasionally patients, while suffering from a severe attack of chilblains, develop stiffness of the interphalangeal joints to a degree not altogether explained by the swelling of the soft tissues. The joints become slightly swollen and the fingers somewhat spindle-shaped. The stiffness of the joints remains during the period in which the chilblains are present. The pathology of chilblains is not fully known, but it is certainly true that failure of the capillaries to respond normally to cold is the outstanding feature. Hallam[11] states that a high/

high percentage of patients with acrocyanosis suffer from chilblains. When discussing the responses of the capillaries to cold, it was stated that marked cyanosis of the skin is abnormal, as although cold dilates the capillaries and slows the blood flow, the oxygen requirements of the cells fall with the temperature. In acrocyanotics the circulation is habitually slow; a further slowing by cold so reduces the supply of oxygen to the tissues that the metabolism of the cells is interfered with and finally chilblains are caused. It seems probable that the mild arthritic changes mentioned above were due to a similar slowing of the blood stream in the tissues of the joints, as these patients were of the acrocyanotic type.

If slowing of the blood stream can cause arthritic changes in joints, any measure which can promote an active flow of arterial blood to the joints should ameliorate the condition. It has been argued that protein shock therapy acts in this way by causing a reaction similar to urticaria, but the reaction is here so complicated that it is difficult to draw any conclusions from it. Two cases, however, recorded by Young[12] of the effects of periarterial sympathectomy on diseased joints, show clearly how beneficial the effect of an increased blood flow may be. One of these cases was that of a destructive osteo-arthritis of the left ankle and tarsus in a man aged 44, and the other a painful con-

dition/

condition of the right knee in a woman aged 65. In both, following periarterial sympathectomy, pain rapidly disappeared and function was restored. The sympathetic produces constriction of the minute vessels, more particularly of the arterioles. Section dilates the vessels and increases the flow of blood to the tissues, and to this action are due the beneficial effects of the operation. It is interesting to note that the second set of nerves which influence the capillaries, namely the sensory nerves, can also produce profound changes in joints. In tabes dorsalis the posterior root ganglia are affected, the regulation of the tissue cells and capillaries by the antidromic influence of the sensory nerves is interfered with, and in the joints trophic changes occur to produce the condition of Charcot's joint.

In the conditions of fibrositis and panniculitis the influence of the capillaries is important, and an example of these conditions will now be considered.

Case 4. Mrs McA. Aged 56.

This patient is somewhat stout, but not unduly so. The subcutaneous tissues are thickened and tender to pressure, particularly over the deltoids, on the outer aspect of the thighs, and in the abdominal wall. There

is stiffness of the arms and pain on movement. Bruising readily occurs, gripping the arm firmly being sufficient to produce it. Petechial haemorrhages frequently appear, most commonly on the legs; the appearance of the haemorrhages is usually associated with an exacerbation of aching in the fibrous tissue. During settled weather she is comparatively well, although she always complains of a "tired feeling." Any change in the weather, and particularly the onset of a cold spell, causes her to suffer great pain.

This history is of a type that is very commonly met with, and the interesting feature in this particular case is the regularity with which the petechial haemorrhages occurred in association with exacerbations of the rheumatic symptoms. The haemorrhages in themselves were few in number and very minute.

When considering the etiology of rheumatism in the fibrous tissues, it is necessary to account both for the original pathological changes and for the periodic exacerbations of the symptoms. How the original changes are caused is not yet clear. Stockman[13] has been unable to detect any organisms in the inflamed areas of panniculitis, and has always obtained negative results from attempted cultures from fresh tissues. He concludes that in panniculitis the fibrosis must be due to an irritant of some kind which acts specially on connective tissue. Whether this irritant/

irritant acts directly on the cells or whether it produces its effects by action on the capillaries is not known, but there is no doubt that when the fibrosis is established capillary instability is a prominent feature. The capillaries in the rheumatic tissue are abnormally sensitive to climatic conditions, and changes in the weather, particularly when due to sudden fluctuations in the barometric pressure, affect the permeability of the capillaries and fluid passes into the tissues. The tissues swell, the sensory fibres are pressed on and aching results. It is not possible to observe directly the changes occurring in rheumatic tissue, but in the white fibrous tissue of scars, which has a similar structure and in which aching sometimes occurs, the abnormal nature of the capillary responses may be observed. When exposed to cold the circulation in the scars becomes slower than that of normal skin and the scars stand out blue against the pale skin. While the capillaries of the rheumatic tissue are undoubtedly abnormal, there is evidence that the vessels of this tissue are not alone affected, but that there is a general instability of the capillaries. The occurrence of petechial haemorrhages is in favour of this. In Tidy's[14] opinion the small size of many spontaneous cutaneous haemorrhages indicates that the blood must have escaped from the capillaries. The blood cells under certain circumstances

are/

are known to pass through the walls of the capillaries, and an increase in the permeability of capillary endothelium of sufficient degree would permit a large number of cells to pass out of the vessels and form cutaneous haemorrhages.

It is probable that the petechial haemorrhages occurring in association with rheumatism are caused in this way, and indicate a general tendency of the capillaries to abnormal permeability. The treatment of rheumatism is usually directed towards improving the circulation in the capillaries. Counter-irritation, radiant heat, and massage all act in this way, and it is by stimulating an active flow of blood to the affected areas that the alleviation of the symptoms is produced.

In the next case to be considered urticaria was associated with marked gastro-intestinal symptoms.

Case 5. Mr B. Aged 46.

This patient, who suffers from frequent attacks of indigestion, ate tinned salmon about seven o'clock one evening. About two o'clock next morning he was wakened by severe abdominal pain. Diarrhoea developed and fluid motions with much mucus were passed. His skin became very itchy and he found that a rash had appeared. When I saw

him/

him the following morning, the diarrhoea had ceased, but there was still abdominal discomfort and the rash was still present. The rash was a "red urticaria". Large red patches were present on the trunk and legs, but there was no whealing. The presence of pre-existing patches of unpigmented skin made the urticaria particularly striking, for in the unpigmented areas capillary dilatation had not occurred, and they stood out dead white against the red background. It has been suggested that errors in pigmentation are due to faulty innervation by the sympathetic system and it is possible that the failure of the capillaries in the unpigmented areas to react in the same way as those of the surrounding skin was due to defective innervation of the capillaries in these areas. The urticaria persisted unchanged for two days; on the third it began to fade and had gone by the fifth day. The patient, however, continued to suffer from indigestion and flatulence for several days. As he had several septic teeth, I advised him to visit his dentist, which he did ten days later. On extracting the right canine an abscess was found at the apex. The same night he had another attack of urticaria and slight abdominal discomfort. About a year before this time he had two attacks of urticaria and diarrhoea. On these occasions crab had been eaten. For several years he has/

has been unable to eat eggs without suffering from abdominal discomfort and shivering and sweating. In addition he has frequent attacks of dyspepsia, for which no cause can be found.

In the present attack the simultaneous appearance of urticaria indicates that the gastro-intestinal symptoms were due to intestinal allergy. It is probable that the minor attacks due to eating eggs were due to the same cause, although on these occasions urticaria did not appear on the skin. The question of intestinal allergy is one of which very little is as yet known, but it is probable that the reaction of the capillaries of the intestinal tract to foreign proteins explains many of the cases of digestive disturbances for which no organic cause can be found. In this case the allergy was acquired as the patient could formerly eat the articles of food which now upset him. I have already stated the opinion that absorption from toxic foci may produce a tendency for sudden capillary reactions to occur. In this case the development of intolerance to certain foods is probably due to the influence of the toxins which were being constantly absorbed from the septic teeth, and the attack following the extraction of the septic tooth, to the sudden liberation of a large amount of toxin into the blood stream. An improvement in general health, and

a/

a diminution in the frequency and severity of the gastro-intestinal upsets occurred following the dental treatment.

No mention has so far been made of the production of ill-health by the abnormal action of the endocrines and the nervous system on the capillaries, but cases of this kind are frequently met with in general practice.

Case 6. Miss C. Aged 21.

This patient is a well-developed girl, but in the vessels of her skin shows evidence of capillary instability. Her hands are always cold and readily become cyanosed. She blushes frequently, and the reddening of the skin is not uniform but has a patchy distribution. She suffers from mucous colitis and dyspepsia. During her menstrual periods the nasal mucous membrane becomes congested and this is often followed by a "cold in the head." Headaches commonly occur during menstruation, and the ears become red and congested. At these times, too, exacerbations of the mucous colitis are common.

Many cases illustrate that the ovarian hormone responsible for menstruation, which produces congestion of the uterine mucosa, also affects the capillaries in other situations. Congestion merely, may be caused, or haemorrhage may result. Bleeding from the nose is common, and bleeding/

bleeding from the ears has been recorded. In the case of a woman who had several teeth extracted, bleeding from the gums recurred four days later on the first day of menstruation. In the condition of so-called "gastrostaxis" bleeding from the stomach may occur at the menstrual period. Moore[15] records a case of Eale's disease in which the recurrent haemorrhages into the interior of the eyes occurred at the time of the menstrual periods. In the above case the congestion of the nasal mucosa and the exacerbations of mucous colitis are due to capillary congestion which has stopped short of actual haemorrhage. Nasal congestion and mucous colitis will be separately discussed.

The capillaries of the nasal mucous membrane are affected by various stimuli. The congestion of monthly occurrence has been attributed by Mackenzie[16] to antidromic stimulation of the trigeminal nerve by the ovarian hormone. To the same cause he attributes the congestive headaches occurring at these times. Foreign proteins may also cause congestion of the nasal mucosa. Hay fever is of course the commonest example of this and is due to direct contact of the pollen with the mucous membrane. Ingested proteins may, however, produce a similar effect. Hill[17] reports a case of a physician whose nasal mucosa became/

became intensely congested if he ate a few strawberries, and less striking examples of this kind are not uncommon. The importance of nasal congestion is the part played by it in the causation of coryza. In the case described above, the monthly congestion of the nose was frequently followed by coryza. Similarly in hay fever bacterial infection commonly occurs. It would appear, therefore, that a state of capillary congestion lowers the resistance of the nasal mucosa to bacterial infection. "Colds" are often caused by passing from a hot stuffy room into the cold outer air, and the congestion of the capillaries of the nasal mucous membrane due to the sudden change of temperature is an important feature in the etiology of these cases.

Of the pathology of mucous colitis little is known. The condition is almost invariably accompanied by neurasthenia or some form of neurosis, and it is probable that the abnormal secretion of mucus and the congestion of the colon are due to the disordered action of the nervous system. When exacerbations occur during menstruation antidromic stimulation of the sensory nerves to the bowel by ovarian hormone may be responsible. On the other hand, the exacerbations may be due to the congestion of the neighbouring pelvic organs, and until more is known of the sensory innervation of the bowel the question cannot be/

be settled. Certainly, however, the sedative treatment of the nervous system will often produce improvement in the bowel condition. The influence of the sympathetic system on the vessels of the gastro-intestinal tract is another subject of which little is known. Alvarez[18] says, "Just as sensitive persons blanch and blush externally; so also they may perhaps blanch and blush internally. It is known that marked changes in the blood supply of the mucosa do take place and they might well help or hinder the mechanism which normally removes gas from the digestive tract; such a mechanism together with air swallowing might explain the sudden attacks of flatulence seen in nervous persons." There is no doubt that further investigation of the innervation of the gastro-intestinal tract will lead to a better understanding of many of the cases of dyspepsia met with in nervous patients.

The cases recorded in this paper have illustrated how abnormal capillary reactions may produce lesions in various regions of the body. The treatment of these conditions was naturally to some extent determined by the site in which the capillary disturbance arose, but with a view to comparison in all the types of cases described, the effects of one form of treatment, namely the administration of calcium, was investigated. In the blood, calcium is present in two forms. About/

About 60 per cent. is in a diffusible form and the remainder in a non-diffusible form combined with protein. If the amount of diffusible calcium is lowered the permeability of the capillaries is increased, while raising the calcium level decreases their permeability. As the retention of calcium in the tissues is associated with the presence of Vitamin D, in the treatment of cases of capillary disorders a preparation of colloidal calcium and Vitamin D given by subcutaneous injection was used.

The use of this preparation of calcium and Vitamin D in many cases of capillary disorders has shown that when once a capillary reaction has occurred, or where gross pathological changes are present in the tissues, little or no benefit is derived from its administration, but if it is given to an individual who is known to be susceptible to abnormal capillary reactions the liability for these to occur is diminished. To consider skin vessels first, patients in whom an urticarial rash had developed were not benefited by the injection of calcium. Urticaria fades of its own accord whether treated or not and calcium does not appear to accelerate the speed of fading. In the case of children, however, who suffer from repeated attacks of urticaria, a number of injections of calcium and Vitamin D at weekly intervals lessens the frequency and severity of the/

the attacks. It is difficult to be sure that the treatment is responsible for the results as children naturally tend to become less liable to develop urticaria. When dealing with traumatic urticaria in adults, however, there is more certainty. Mosquito bites are a form of traumatic urticaria and many people suffer severely from them every year when on holiday. Two or three injections of calcium and Vitamin D were given to several such patients during the week immediately before they went on holiday, and in several instances freedom or diminished severity from the reaction from insect bites was reported. It appears, therefore, that by raising the calcium balance the susceptibility to urticarial reactions can be diminished, but that when urticaria has developed it is not affected by the administration of calcium.

The treatment of chilblains with calcium and Vitamin D during the winter when the condition is fully developed is rather disappointing, although there is some reduction of the swelling, and healing of broken skin is assisted. If, however, six or more weekly injections are given prior to the onset of cold weather the benefit derived is considerable. Chilblains may not develop in previously mild cases, and the severity of other cases is reduced. In fibrositis and panniculitis extensive fibrosis is present, and it is not/

not to be expected that calcium therapy would reduce the fibrosis. The exacerbations of aching, however, in these conditions are due to the abnormal permeability of the capillaries in the affected areas, and with a view to investigating whether this might be controlled, calcium was administered to several "rheumatic" cases during exacerbations. The results were entirely negative, and this supports the view expressed above that when gross pathological changes are present in the tissues calcium therapy is ineffectual.

Asthma and hay fever I have not found to benefit from calcium administration, although good results have apparently sometimes been obtained from this treatment in these conditions. Mucous colitis, however, has responded to calcium therapy. It is difficult in this condition to assess the results of treatment as any new method of attack meets with the approval of the patient and an initial improvement is usually reported. In several instances, however, a definite diminution in the amount of mucous secretion and improvement in general health resulted and were maintained. These patients were all young; long-standing cases in older patients were unaffected.

The vasomotor disturbances associated with menstruation can sometimes be controlled by calcium therapy. In the case recorded/

recorded of the girl who suffered from nasal congestion, headaches, and exacerbations of mucous colitis during menstruation, two injections of calcium and Vitamin D were given in the week preceding menstruation. Nasal congestion did not occur on this occasion, and headache was not experienced. Four further injections of calcium and Vitamin D were given at weekly intervals and the colitis gradually improved. At the next menstrual period there was again freedom from symptoms, and this improvement has now been maintained for several months. In several other cases of this type calcium therapy has been successful, and it is therefore indicated in the treatment of vasomotor disturbances associated with menstruation.

Dilatation of the capillaries is a physiological response to the tissue demand for an increased blood supply. The vascular responses to cell injury are in the main beneficial as the active blood flow increases the defensive powers of the tissues. In certain circumstances, however, harmful capillary congestion occurs; the flow of blood becomes very slow and the metabolism of the cells is affected. Increased permeability of the capillaries causes swelling of the tissues and the blood flow is further interfered with. It is by controlling the permeability of the capillaries that calcium therapy produces beneficial effects. The liability for/

for harmful capillary reactions to occur is increased in patients who have an unstable capillary system. The most important causes of capillary instability are the slow absorption of bacterial products from toxic foci, abnormal endocrine secretion, and functional disorders of innervation associated with a neurosis. It must be remembered, however, that apparent instability of the capillaries may be due to more complex changes in the tissue cells themselves.

In conclusion, I am fully aware that the study of abnormal capillary action is still in its infancy, and that there may be many factors involved of which we have as yet no cognisance. It is certain, however, that the reactions of the capillaries are an important factor in the pathology of many conditions.

Further investigation of these reactions, particularly in the deeper structures, may yield information which will be of great value in the understanding of early disease processes.

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