ON THE CLINICAL RECOGNITION OF STRUCTURAL DISEASE OF THE PERIPHERAL VESSELS*

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Impairment of the circulation to a limb may result in two ways: from structural disease of the vessels with a consequent permanent reduction in their calibre, or from excessive narrowing (spasm) of vessels that are yet able widely to expand. A first and essential step in understanding most disorders of the peripheral circulation is to determine whether any structural lesion of the vessels is present or not, and if so, its extent. Much indispensable information may be gained from a simple examination of the patient, and this may be amplified and rendered more precise by the use of certain tests. Many of the methods now employed are little known, and some confusion seems to exist as to the interpretation of others. During recent years considerable attention has been devoted to the peripheral circulation in health and disease by workers in this department, and the present seems an opportune time to give an account of the methods we have found to be most serviceable in identifying structural disease of the vessels.

PHYSICAL EXAMINATION OF THE LIMBS

Abnormalities of appearance of the extremities in vascular diseases are chiefly of three kinds: gangrene, indolent ulceration, and colour changes; and these may all appear in affections of the arteries that are either primarily spasmodic or primarily structural. Gangrene implies a prolonged and complete interruption of the blood supply to the affected area; and while possibly it is invariably associated with thrombosis of the vessels concerned, such a change may be restricted to the site of the lesion, the vessels elsewhere being patent and the main malady essentially spasmodic. Indolent ulceration may be due to an impaired blood supply from spasmodic or structural narrowing of the vessels, but it also occurs in a number of low-grade chronic infections. Thus widespread structural disease of the vessels may be suspected, but cannot be diagnosed from lesions of these kinds.

Abnormalities of colour are of two kinds: change in depth and change in tint. In the absence of severe anaemia abnormal pallor of an extremity indicates emptiness of the minute vessels. Such a condition usually results when blood is massaged out of a part by movement, and its inflow is prevented by spasmodic or organic obstruction of the arteries; less commonly, it may result from active contraction of the minute vessels, as in Bier's spots and in certain forms of the white finger of Raynaud's disease.¹ Increased depth of colour is due to a dilatation of the capillaries and venules of the skin as a result of injury, such as is probably produced by impaired blood supply, long-continued cold, and possibly low-grade inflammation. Cyanosis confined to one or more limbs is due to local slowing of the blood flow relative to the oxygen requirements of the skin. When a limb is cold its arteries or arterioles are narrow, such narrowing being excessive in patients suffering from Raynaud's disease¹ and acrocyanosis²; in cold skin cyanosis is frequently due to constriction of arteries that are yet capable of dilating widely. In a limb that has been warmed it may be assumed that normal vessels tend to be dilated; cyanosis in such a limb provides strong presumptive evidence that the arteries cannot fully expand and

are structurally diseased. In assessing the significance of cyanosis it is to be remembered that with equal rates of blood flow high-coloured skin will be bluer than pale skin, for the vessels that contribute most to the excessive coloration of the skin—the venules—are those in which the blood has been largely robbed of its oxygen.

Postural changes in skin colour are common in structural disease of the vessels, but are by no means confined to these. A deepening and blueing of the skin when the limb is dependent is commonly due to passive widening of toneless minute vessels consequent on the hydrostatic increase of venous pressure. Such a colour change is seen in any form of long-continued injury to the skin, as, for example, in skin that has been reddened by exposure to ultra-violet light. Conspicuous pallor of the skin when a limb is raised and maintained for a few minutes some distance above the level of the heart is strongly suggestive of a structural lesion of the vessels; and the height at which such pallor occurs is used as an index of the degree of disease by Buerger.³ When a limb is raised blood drains from the skin, and conspicuous pallor will occur if blood fails to enter freely from the arterial side, as it may if the head of pressure is reduced by structural changes in the vessels. The pallor is probably associated with grossly deficient blood flow to the skin, for it has been observed by Buerger and ourselves to be followed by reactive hyperaemia when the foot is again lowered.

The rate at which colour returns to skin that has been blanched by pressure is frequently used as an index of the rate of the cutaneous blood flow. It is an unreliable test, because the return of colour is often from the surrounding venous plexuses rather than from arteries, and the rate of return then depends chiefly on the pressure in those plexuses. If a warm limb is congested by hanging it down, and its circulation is arrested while the skin is full of blood, the colour returns quickly to an area of skin blanched by pressure with the finger, although circulation to the limb has ceased.

Temperature

Perhaps the most important indication we possess of the adequacy of the blood flow through a limb is the temperature of the limb's surface, for the difference between this temperature and that of the atmosphere is governed by the rate of blood flow through the skin.

Before using the skin temperature as an index of vascular disturbance it is essential to realize that it has wide fluctuations in health; it is largely by variations in cutaneous blood flow that body temperature is regulated. Exposure of the body to cold has a twofold effect on the circulation to the skin. First, the cooling of the superficial arterioles tends directly to narrow them, and secondly, a generalized cutaneous constriction is set up through the vasomotor nerves, evoked in part reflexly by the stimulus of cold to the skin, and in part by the action of cool blood returning from the skin on a central mechanism.⁴ Thus it comes about that when the air is cool the peripheral vessels are constricted and the extremities are cool; when the air is warm the cutaneous arteries and arterioles dilate and the extremities are warm.

The level of air temperature necessary to produce vasodilatation and warm extremities varies from subject to subject; it largely depends on the warmth of clothing. Persistently cold extremities may be due either to vascular disease or to high vascular tone, and the latter may be normal or abnormal according to the circumstances in which it is displayed. Thus coldness of the extremities does not suffice for the diagnosis of arterial disease or arterial spasm. Of greater significance is an inequality of temperature between two symmetrical limbs similarly treated, and exposed for the same length of time. In

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these circumstances the smaller blood flow through the colder limb must be ascribed to a local cause, and, in the absence of disuse, consequent on manifest diseases of the nervous or locomotor systems, unilateral coldness is almost always, if not always, due to structural disease of the corresponding blood vessels.

Nevertheless, although it is the rule for a limb more affected by structural vascular disease to be persistently colder than its fellow, the reverse is occasionally found. In two of our patients with thrombo-angiitis the limb carrying the more grossly diseased vessels has been persistently the warmer (for example, Case 1 of table). Morton and Scott⁵ have noted the same phenomenon in some cases of endarteritis. They appear to consider that it is usual for a limb to be warm when its vessels are affected by structural disease, provided that this is not extreme, and they ascribe coldness under these circumstances to a reflex vaso-constriction. A little consideration shows, however, that such a conception is as yet unnecessary, and therefore undesirable; for, unless the body is hot, sympathetic tone is always present, and experiment goes to show that it affects symmetrical limbs equally. It is therefore to be expected, and is indeed the rule, that when an additional structural change is present in the vessels of one limb the circulation through that limb will be slower than in its fellow. When the limb having the more affected vessels is the warmer, then some other factor must be called to account for this. There is as yet no reason to suppose that vasomotor tone is locally withdrawn to compensate for structural disease, and we suggest that in such warm limbs the circulation is largely maintained by the opening of collateral channels lying particularly in the skin or subcutaneous tissues.

Pulsation of the Arteries

Arterial pulsation may be detected with the finger or by means of Pachon's oscillometer. The latter method, in general, confirms palpation, but in addition will record pulsation in situations such as the calf of the leg, where the vessels lie deep and are inaccessible to the finger; moreover, being instrumental, it is more reliable in demonstrating inequalities of pulsation on the two sides. The readings obtained are subject to conspicuous errors, however, and the instrument must be used with corresponding caution. In normal subjects it is usual to feel pulsation in both the large vessels at the wrist and at the ankle, and to record pulsation as far distally as these points. It sometimes happens in normal subjects, and in cases of Raynaud's disease, that the pulse cannot be felt in one or more of these vessels when the limbs are cold, and it is therefore essential in determining the patency of the vessels that the limbs should be warm in order to relax vessels that are capable of opening up.

Babinski and Heitz⁶ observed a number of cases of functional coldness of one limb following war wounds, where the oscillometric pulsations were greatly reduced in the injured limb when this was cold. On soaking the limbs at 40° C. for ten minutes the pulsations became as great in the injured as in the sound limb, whereas in cases where the main artery to the limb had been tied, the pulsations remained small after the limb had been warmed. We would suggest, therefore, that when testing the limbs for pulsation of the vessels, it is of the greatest importance before concluding that a pulse is absent or diminished to make the patient feel warm, and to soak his limbs in water at 40° for ten or more minutes before examining the vessels. The failure of pulsation in an artery of a limb when body and limb are warm is the most certain sign we possess of structural disease in that vessel.

It is important to realize, however, that pulsation may be retained in one or more of the main vessels of the foot

or hand after the smaller arteries have become extensively diseased⁷; and it should also be recognized that the circulation to a limb may be almost normal in the absence of pulsation in its vessels, as is the case in the legs of patients with coarctation of the aorta.⁸

Allen's Test.—Allen⁹ has described a simple method for recognizing an organic obstruction of the ulnar or radial artery at, or distal to, the wrist. After the patient has clenched both hands tightly for one minute, the observer compresses digitally both radial arteries at the wrist, and the patient's hands are relaxed. When the ulnar artery is patent, colour quickly returns to the hands, and is then little changed by release of the radial. When the ulnar artery has been obliterated by disease, then the colour returns only slowly to the hand, until the radial is released, when the palm and fingers flush brightly. To test the patency of the radial artery the same method is used, though with ulnar compression. In practice we have found the rate at which the colour returns to normal hands to be very variable during compression of the radial artery; when, however, there is a striking difference between the behaviour of the two hands, then the test provides strong evidence that the ulnar (or radial) artery on one side is obliterated.

Capillary Pulsation

In extremities that have been warmed by immersion in water at 42° to 45° for ten minutes, it is usually possible in normal subjects to elicit capillary pulsation in the palmar surfaces of the hands and plantar surfaces of the feet by light pressure with a glass slide.¹⁰ The presence of capillary pulsation indicates that the arteries and arterioles supplying the corresponding area of skin are patent, and is a valuable sign that there is no appreciable structural defect of any of these vessels. Some find difficulty in detecting this pulsation, however, and its absence should not be considered adequate evidence of structural blocking of the vessels.

The Veins

An examination of these vessels is sometimes important in identifying thrombo-angiitis, for as Buerger³ emphasized, the veins become thrombosed in many cases. The veins share in the general vascular relaxation produced by warmth, and the most satisfactory method of demonstrating the superficial venous plexus is to immerse the foot for ten minutes in water at 35° to 40°, and then to distend the veins by obstructing them in the leg with pneumatic pressure of 60 to 70 mm. Hg.

From this brief account it may be seen that much indispensable information may be gathered from relatively simple clinical methods, and a large proportion of cases of structural disease of the vessels may be diagnosed in this way. There are cases in which information thus gained is equivocal, and the diagnosis remains in doubt. Moreover, it is not enough merely to identify a permanent blocking of the vessels; it is essential for purposes of treatment to recognize, so far as possible, the extent of the disease, and the measure to which it has been corrected by the opening up of collateral channels. Several tests now to be discussed have been devised to meet these requirements.

TESTS FOR STRUCTURAL DISEASE OF THE VESSELS

I. Intermittent Claudication

Intermittent claudication is a term used to indicate a condition in which pain develops in the muscles of a leg and causes limping on walking. This pain frequently becomes so severe that the patient has to stop, but after a few minutes of rest it disappears, and exercise can be resumed. The mechanism of intermittent claudication has been fully discussed in an earlier publication.¹¹ The

appearance of this highly characteristic pain, in the absence of severe anaemia, in which it also occurs,¹² may be taken as an indication that structural disease of the corresponding vessels is present; and the degree to which exercise is curtailed by pain provides an approximate index of the extent to which the muscular circulation is impaired. A history given by an intelligent patient is usually sufficient to elicit these points, but it is important to recognize that in the presence of gross disease of the vessels pain may be prevented from developing during exercise in one of two ways. In the first place the exercise may never be sufficient to elicit pain; this is often the case when two legs are unequally diseased, and the curtailment of exercise by pain in the more diseased limb prevents the development of pain in its fellow. Secondly, when only one limb is diseased, the development of pain in this may be prevented by a peculiarity of gait, the work being done mainly by the healthy leg or by an unusual group of muscles that is well supplied by blood. So it is sometimes desirable to test the development of pain under standard conditions. If, after the circulation to the leg of a healthy subject has been arrested, the ankle-joint is repeatedly and fully extended against resistances at the rate of one complete movement per second, pain begins in the calf muscles; or if the joint is flexed against resistance it begins in the anterior tibial muscles. It comes in twenty to thirty seconds, and becomes unbearable after seventy to ninety seconds, disappearing in five seconds or less after the circulation is released.¹¹ If a patient with diseased vessels works his leg in the same way but without circulatory arrest, then the times taken for pain to begin, to become intolerable, and to disappear after exercise is stopped, provide guides to the adequacy of muscular blood flow. As the times of onset and intolerance of the pain depend on the amount of exercise undertaken, it is usually desirable to compare the times so elicited with the times obtained when the patient repeats the exercise in the same limb with its circulation arrested; a period of fifteen or more minutes should be allowed to elapse between these tests.

II. *The Effect on Skin Temperature of Removing Sympathetic Vaso-constrictor Tone*

The capacity of the skin vessels to dilate may be tested by following thermo-electrically the course of the skin temperature when sympathetic tone is removed. To obtain a striking effect it is necessary that vaso-constrictor tone should be initially high, as when the subject has been previously lying thinly clad at a room temperature of 16° to 18° C. On removing sympathetic tone the extremities in normal subjects quickly become warm, and the capacity of the vessels of the limb to convey blood is best gauged by the final level of temperature so attained. The rise of temperature almost always begins and is most rapid in the tips of the digits, and follows more slowly in the proximal parts of the limbs.¹⁵ Sympathetic vaso-constrictor tone can be removed by paralysing the sympathetic fibres by means of a local anaesthetic. Thus sympathetic fibres may be blocked by injecting novocain or a similar preparation around the appropriate ganglia of the sympathetic chain (White¹³), around the mixed nerves, (Lewis,¹ Morton and Scott⁵) or, in the case of the lower limbs, into the spinal canal (Morton and Scott,⁵ Telford and Stopford¹⁴). A simpler method of releasing sympathetic tone, and one causing less discomfort to the patient, is to raise the body temperature, either by enclosing the subject with the exception of the limbs to be examined in a chamber heated by electric lights (Lewis and Pickering¹⁵), or by immersing one or both of the remaining limbs in water at 42° to 45° (Pickering,⁴ Gibbon and Landis¹⁶).

These methods of producing vaso-dilatation in the limbs differ in efficiency in the upper and lower extremities. Many cases of Raynaud's disease examined when the vessels are in spasm show no rise of skin temperature of the little finger when the sympathetic fibres of the ulnar nerve are blocked by novocain, while these same patients show a full and normal vaso-dilator response to warming the body; this difference has led us to suggest that the sympathetic contains vaso-dilator as well as vaso-constrictor fibres.¹⁵ In the lower limbs, on the other hand, Landis¹⁷ has observed three cases of acrocyanosis, which failed to respond to warming of the body, yet showed a normal response to blocking of the sympathetic fibres; working independently we have found this to be true for some normal subjects also. In identifying structural disease of the vessels, body-warming is adequate and is the simplest method to use in the case of the upper limbs; nerve anaesthetization is the best method in the lower limbs.

Some confusion seems to exist over the interpretation of this test. In normal subjects exposed to air temperatures of 18° to 20°, the skin temperature of the extremities rises to 32° or more when the peripheral vessels are fully dilated by either of the methods described. The measure of organic obstruction to the flow of blood to the skin is gauged, in this test, by the deviation of the final level of skin temperature attained from the normal of 32° and not by the total rise of skin temperature, the latter depending largely on the initial temperature of the extremities.

Many workers^{5, 14} consider that if, in this test, a rise of skin temperature is obtained, then the condition of the vessels is one characterized ordinarily by spasm, and that the degree of rise indicates the measure of spasm. It is to be pointed out that if this interpretation is to be adopted then the vessels of every normal subject would have to be regarded as in a condition of spasm, and the word would lose its proper significance. A rise of skin temperature occurring after paralysis of the sympathetic fibres indicates that the vessels were constricted initially, at least in part, by sympathetic tone. It is not to be overlooked that sympathetic tone is a normal phenomenon, and the most important single factor in the control of body temperature; a rise of temperature shows simply that the vessels have the capacity to dilate, but if the dilatation is imperfect the temperature reached may show it, and indicate the degree to which they are permanently constricted by structural disease of their walls.

The test gives important indications for treatment. If a lesion is present in an extremity that is habitually cool but which becomes warm during the test, then it is reasonable to anticipate some improvement to result from the removal of sympathetic tone. As a temporary therapeutic measure we have frequently found it sufficient to keep the body warm by hot-water bottles and blankets, the limb being uncovered or covered lightly. A more lasting effect may be obtained from sympathectomy. In assessing the probable value of this operation it is well to be cautious, for the immediate effects are more striking than the later, the vessels regaining a certain measure of tone after sympathectomy.¹⁸ Our experience agrees with that of Morton and Scott,⁵ who consider that if in the test a skin temperature of less than 28° C. is finally reached then sympathectomy is inadvisable.

*The Reactive Hyperaemia Test**

When the circulation to a warm normal limb is arrested for five minutes and released a bright flush (reactive hyperaemia) spreads at once throughout the limb, reach-

* This important test was mentioned but not discussed in an earlier publication.¹¹

ing the tips of the digits in two to five seconds. The rapidity with which this flush appears in any piece of skin depends on the patency of the vessels leading to it. In using this test to detect structural lesions of the vessels it is essential that the vessels of the limbs should be dilated, which can be ensured by maintaining the body and limbs warm. If the limbs are cold, then in normal subjects, and especially in subjects with spasmodic affections of the arteries (Raynaud's disease and acrocyanosis), the arteries or arterioles of the skin are constricted and the appearance of the flush is delayed and may be prevented. A test of this kind introduced by Moszkowicz¹⁹ fell into disrepute for the very reason that he failed to control the temperature of the limbs. One other precaution must be taken—namely, to empty the limbs of blood before arresting the circulation to them; for if the skin vessels are engorged with blood throughout the period of vascular occlusion, plasma is lost from the contained blood, and the normal vessels are left packed with blood corpuscles, a condition of stasis which greatly delays the return of fresh blood to the skin at the release.

The test should be performed in a room at 20° or over, and if the subject is not already comfortably warm he

patients, the limbs being kept warm by covering with blankets and hot bottles. (It should be remembered that it is easy to burn the skin with a hot bottle when the circulation is deficient.)

The reactive hyperaemia test demonstrates whether the circulation to the skin is reduced by the presence of structural disease of the vessels. All of our patients who were known, on other grounds, clinical or pathological, to have structural lesions of the vessels, and who had complaints referable to an impaired blood supply to the skin, have shown an abnormal response to this test. A few examples are given in the accompanying table.

In two of our patients pulsation was absent in all the vessels of a limb while the reactive hyperaemia test was normal; in both there was reason to believe that a localized thrombosis had occurred in the main vessel at its origin from the aorta, the vessels distally being healthy. The more completely investigated of these cases was a man found to have an aneurysm of the abdominal aorta in 1921, the femoral pulses being then present. The left femoral pulse disappeared in 1923, the right between 1927 and 1931, after which he had pain in both legs on walking. When examined in December, 1931 (then aged 52), the lower limbs were warm and of

Table Comparing the Results of Clinical Examination with the Times of Reactive Hyperaemia in Patients with Structural Vascular Disease

Case	Diagnosis	Age	Leg	Arterial Pulsation				Excursions of Oscilometer			Time of Reactive Hyperaemia			Remarks
				Fem.	Pop.	Post. Tib.	Dor. Ped.	Knee s.d.	Calf s.d.	Ankle s.d.	Calf min. sec.	Heel min. sec.	Toes min. sec.	
1	Thrombo-angitis	40	R L	+	+	+	+	1 9	1 8	0 2	0 15	0 45 0 5	0 50 0 10	Intermittent claudication right leg. Right leg persistently warmer than left.
2	Thrombo-angitis	25	R L	+	+	—	—	10 3	6 0	2 0		0 4 0 15	0 10 0 40	Claudication left leg. Healed ulcers left toes. Right toes reach 31°. Left 29° after body warming. Sympathectomy gave a fair result.
3	Thrombo-angitis	47	R	+	+	—	—	5½	1½	0	0 5	0 25		Left leg amputated three years before. Extensive gangrene dorsum right foot. Successful amputation lower third of right leg.
4	Diabetic gangrene	64	R L	+	—	—	—	0 1	0 0	0 0	0 5 0 5	0 37 0 13	1 30 0 35	Gangrene three right toes. Successful amputation lower third of thigh.
5	Senile gangrene	52	R L	+	+	+	—	6 6½	2½ 4	1 1		0 5 0 5	0 55 1 0	Bilateral intermittent claudication. Healed ulcer right toe.
6	Diabetic gangrene	74	R L	+	+	—	—	4 2	1 0	0 0		0 5 0 11	0 15 0 28	Gangrene of right great, third, and fourth toes. Successful amputation of these toes. The flaps became septic, necessitating removal of a metatarsal.

must be made so by warming him with hot-water bottles and blankets. If the upper limbs are being examined the patient may be sitting; if the lower limbs then he should be lying down. The limbs are warmed by immersing them for ten minutes in water at 35°; they are then lifted high out of the water in order to pale the skin, and the circulation is abruptly arrested by inflating to above systolic pressure a sphygmomanometer cuff wrapped around the upper arm or thigh. The limb is returned to the water bath, and after four and a half minutes is lifted out, laid horizontal in a good light, and dried; it should be pale still. A half-minute later the circulation is released and the course of the flush observed. When the vessels are patent—that is, in normal subjects and patients suffering from uncomplicated Raynaud's disease and acrocyanosis—the flush reaches the tips of the digits in less than five seconds, is bright in colour, and reaches a maximum intensity in fifteen seconds or less, and fades quickly. In subjects with structural disease of the vessels the flush spreads slowly and in patches, and may not appear in the tips of the digits until a minute or more after circulatory release. In these cases, too, the flush is commonly a little cyanotic in tint, and often lasts for very long periods of time.

The manner of this test may be modified to suit individual cases provided that the precautions emphasized are borne in mind. Thus it may be made upon bed-ridden

good colour, though no arterial pulsation was palpable at any point. The reactive hyperaemia test was normal, a bright flush appearing in the toes within five seconds of circulatory release. Five days later he died from uraemia; a large aneurysm of the abdominal aorta was found completely filled with laminated clot, the circulation to the legs being adequately maintained by large anastomotic channels. The vessels were dissected in the length of the leg by Dr. Ronald Grant and found to be healthy. Although this patient suffered from intermittent claudication, indicating that the blood supply to the muscles of the legs was inadequate to heavy demands of exercise, he had no symptoms or signs referable to the skin. The normal reactive hyperaemia time must be ascribed to the large collateral supply to the skin, and to the healthy state of the vessels distal to the point of circulatory arrest (the thigh).

The advantage of the reactive hyperaemia test is that it requires no apparatus except that which is readily available to the practitioner, and is, in our experience, as delicate as any single test yet devised. For the simple purposes of diagnosis we regard it as likely to supplant, almost completely, all tests depending on simple release of vasomotor tone. Another point in its favour is that it gives us an indication of the lowest level for amputation that is consistent with survival of the skin flaps. At the moment the site for amputation is usually selected

on the basis of average results in an experience of a large number of cases of similar type; occasionally it is selected by ascertaining the lowest limits of arterial pulsation. When amputation is made at a low level in order to give the patient a relatively useful limb the flaps not infrequently become gangrenous, and a second and higher amputation is necessary. Moszkowicz¹⁹ originally suggested that the site of amputation should be decided by the absolute lower limit of the reactive flush, a suggestion which has been found to be impracticable. We have already indicated why this test is unreliable; if due precautions are taken the flesh extends eventually to all parts of the living skin. It is clear that if the test is to be of value in selecting the lowest safe site for amputation then some arbitrary time limit for the appearance of the flush must be set that is compatible with the healing of such skin when cut into flaps. At the moment we cannot state what this time is with finality, but we suggest as a working basis that if a bright flush appears in the heel within fifteen seconds of circulatory release then amputation just above the ankle is safe, and if the flush appears in the toes within twenty seconds then amputation of the toes is likely to be successful. Illustrative cases supporting this suggestion are Cases 3 and 6 in the table.

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STUDIES ON THE AETIOLOGY OF BLOOD DISEASES

A PATHOGENIC AGENT IN NORMAL HUMAN BONE MARROW

BY

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In January, 1932, we began researches on the aetiology of pernicious anaemia and acute leukaemia. The work is still incomplete, but since there has been a compulsory break in the course of our investigations we wish to report the results so far obtained. In our experiments we have used rabbits, and we have tested the effect of intrathecal injections of bone marrow and blood obtained from human cases. All experiments made with blood have been completely negative; with bone marrow the results have been striking.

In each experiment with bone marrow a little marrow was ground in saline until a fine emulsion was formed; then into each rabbit 0.3 c.cm. of the emulsion was injected through the occipito-atlantal membrane into the theca. Only rabbits weighing 2,500 to 3,000 grams were used. Cultural tests were made of all inocula. Cerebrospinal fluid and portions of brain were taken post mortem from all animals that had received injections, and these,

too, were tested by cultural methods. We shall place on record only experiments in which all cultural media used in the tests remained perfectly sterile. The injection of bone marrow emulsion was followed by an incubation period of from a few days to three weeks; then, in almost all our experiments, a very characteristic picture developed. As a rule, the first symptom to appear was a paresis of the hind legs. In a few of our experiments, however, the earliest symptoms appeared in the muscles of the neck, spasmodic contractions pulling the head into the most grotesque attitudes. Rabbits in which symptoms appeared first in the muscles of the neck showed abnormal voracity, whereas those of the other type lost appetite and weight. In some rabbits symptoms progressed for a time, and then remained stationary or even disappeared; in others disability progressed steadily until death, which occurred within a few days or weeks of the date of the injection. We give in briefest outline a few typical protocols:

EXPERIMENT I

Test of Bone Marrow from a Case of Acute Leukaemia

Rabbit 252.—January 14th, 1932, injection; January 28th, complete paralysis of hind legs; February 10th, moribund, killed.

EXPERIMENT II

Test of Bone Marrow from a Case of Acute Leukaemia

Rabbit 300.—July 28th, 1932, injection; August 9th, complete paralysis; August 10th, moribund, killed.

Rabbit 301.—July 28th, 1932, injection; no symptoms developed.

Rabbit 302.—July 28th, 1932, injection; August 9th, paralysis of hind legs; August 18th, complete paralysis; September 16th, moribund, killed.

EXPERIMENT III

Test of Marrow from a Case of Pernicious Anaemia

Rabbit 299.—July 26th, 1932, injection; August 19th, paralysis of hind legs; August 29th, dead.

EXPERIMENT IV

Test of Marrow from a Case of Pernicious Anaemia

Rabbit 387.—November 15th, 1932, injection; December 5th, complete paralysis; December 20th, dead.

Rabbit 288.—November 15th, 1932, injection; no symptoms developed.

It is evident that in rabbits we have produced a definite encephalitis by the intrathecal injection of bone marrow taken from cases of pernicious anaemia and acute leukaemia. We have tried to find whether this encephalitis is transmissible from rabbit to rabbit. We have taken bone marrow, brain, and liver from encephalitic animals, and of each of these we have made emulsions which we have injected intrathecally into fresh rabbits in 0.3 c.cm. doses. The following are summarized protocols of the experiments.

EXPERIMENT V

Rabbit 305.—August 29th, 1932, injection of bone marrow from Rabbit 299 (pernicious anaemia); no symptoms developed.

Rabbit 306.—August 29th, 1932, injection of brain of Rabbit 299; September 12th, spasmodic contraction of muscles of the neck, distorted position of head, frequent rotations round the body axis, abnormal voracity; September 15th, moribund, killed.

Rabbit 307.—August 29th, 1932, injection of liver of Rabbit 299; September 1st, complete paralysis; September 3rd, moribund, killed.

EXPERIMENT VI

Rabbit 317.—September 15th, 1932, injection of bone marrow of Rabbit 306, an animal which represented those of the first passage; October 6th, paresis of forelegs; October 15th, moribund, killed.

Rabbit 318.—September 15th, 1932, injection of liver of Rabbit 306; October 6th, paresis of hind legs; October 10th, killed.