STUDIES IN DENERVATION

B.—THE CIRCULATION IN DENERVATED DIGITS

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IN his address, *The Relation of Physiology to Medicine*, Lewis (1939) has suggested that one of the functions of a good hypothesis is to stimulate further investigations. Such an hypothesis was presented by Lewis and Pickering (1936) in an endeavour to explain why sympathectomized limbs stay warm while denervated digits become cold. The present paper, which was directly stimulated by their hypothesis, may be introduced by a brief survey of the literature to ascertain if any clues to an alternative explanation can be found.

Previous to the work of Lewis and Pickering only Goltz (1874) seems to have been impressed by the paradoxical nature of the facts. He found that after sciatic nerve lesions in dogs the denervated limb was first warm but became cold in the course of two to four weeks. Claude Bernard, however, had shown that sympathectomy caused vasodilatation in the rabbit's ear. To explain this Goltz conjectured that the initial vasodilatation in the limbs of his dogs and the vasodilatation in the rabbit's ear might be due to traumatic excitation of sympathetic vasodilator fibres. He therefore designed the crucial experiment of stimulating the sciatic nerve and found that this produced vasodilatation. Bayliss (1901) was later to show that the result was due to anti-dromic impulses but Goltz, because of the unfortunate (but not uncommon) coincidence of a mistaken theory and a misinterpreted crucial experiment, was led into the error of believing that the coldness of limbs following section of peripheral nerves was due to a paralysis of sympathetic vasodilator fibres. Nevertheless, despite the seventy years that have passed, ready assent may still be given to Goltz's opinion of the problem for he states that it caused him much worry and many sleepless nights.

Lewis and Pickering in their paper of 1936 resolved the problem with Euclidian succinctness. They state "... while loss of sympathetic supply causes the corresponding fingers to be in general warmer than they otherwise would be, loss of all nerve supply causes the corresponding fingers to be in general colder than they otherwise would be.

And, since with combined loss of both motor and sympathetic supply the digits remain warm, it seems that the sensory nerve loss must be an important factor in determining the persistent coldness in cases of mixed nerve lesions." They were also able to bring evidence as to the mechanism by which this factor operated. They showed that after peripheral nerve lesions the vasodilator axonal reflex induced by cooling disappeared at approximately the same time as the digits became cold. This "chief cause of the lowered skin temperature" was, they believed, augmented by the increased tone of the vessels due to section of the sympathetic fibres and by the inactivity of the adjoining muscle. Somewhat prior to the publication of the above paper Grant *et al.* (1931-3) and Grant (1935) reported a very full investigation of the effects of various types of denervation of the rabbit's ear. Confirmation was given to the fundamental principle enunciated by Elliott (1905) that degenerative section of the sympathetic fibres causes the blood vessels to contract with greater irritability and persistence in the presence of adrenaline than does preganglionic section. That a similar hypersensitivity develops in the human has been established by Freeman, Smithwick and White (1934). Grant further extended his observations to include section of the sensory fibres supplying the ear and found that this did not alter the state of the circulation if degeneration of the sympathetic fibres had occurred. The blood flow to such an ear was found to be very variable, being diminished if the animal was excited or if the ear was exposed to a cool environment while at other times the vessels were almost fully dilated. Ascroft (1937) using the limbs of monkeys has confirmed most of Grant's findings. Of particular interest is his reaffirmation of the fact that the results of lesions of mixed nerves do not differ, so far as the circulation is concerned, from those of degenerative lesions of the sympathetic fibres. Ascroft was particularly impressed by the hypersensitivity displayed by these preparations to the local vasoconstricting action of cold. Also pertinent is his finding that degeneration of the sensory fibres produced by excision of the posterior-

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root ganglia was without apparent effect on the circulation of the limb.

The above observations of Grant and Ascroft together with the finding of Fatherree *et al.* (1940) that the digits of humans in cases of peripheral nerve lesions show a high degree of sensitivity to adrenaline suggest that the hypersensitivity produced by degeneration of the sympathetic fibres may be the cause in lesions of mixed nerves of the habitually cold fingers described by Lewis and Pickering. This explanation has been advanced by Atlas (1938) on the basis of adrenaline sensitization and is rendered the more probable if under the term sensitization is included the increased vasoconstriction to cold.

Such an hypothesis does not solve the conundrum quoted above from Lewis and Pickering, i.e. the difference between the effects of sympathectomies and peripheral nerve lesions, but it will be noted that they did not distinguish between pre- and post-ganglionic sympathectomies. Thus their observations on limbs with a motor palsy plus a sympathectomy are not pertinent as these were made on lower limbs and the sympathectomy being preganglionic did not produce degeneration of the peripheral sympathetic fibres. Nevertheless there is a general agreement that a stellate ganglionectomy in the human produces an habitually warm hand, and failure to do so has been ascribed to the vascular defect for which the operation was performed. Observations on individuals with normal vessels are scanty but Lewis and Pickering (1931-3) illustrate in their Fig. 4 a case in which the vessels were described as being normal and in whom a periarterial sympathectomy and a stellate ganglionectomy had been performed. This subject in a room at 15° C. showed a persistent vasoconstriction in the digits of the operated limb during the 85 minutes of observation despite body warming and vasodilatation in the other hand. Lewis (1937-8) has referred to another case with normal vessels in whom a stellate ganglionectomy was performed to relieve retinitis pigmentosa and in whom the sympathectomized digits were colder than the normal digits when exposed to a cold environment. Conversely Fig. 1 of Fatherree *et al.* (1940) and Fig. 25 of Duthie and Mackay (1940) demonstrate that the vessels of digits denervated by peripheral nerve lesions may be dilated. Such cases suggest that even in the human there is no profound difference between the effects of stellate ganglionectomy and peripheral nerve lesions and the evidence suggests that the loss of afferent fibres is of no vital consequence to the circulation.

It seems logical therefore to enquire further into the assumption made by Lewis and Pickering (1936) that limbs subjected to stellate ganglionectomy and to peripheral nerve lesions differ only in that the latter have degeneration of the sensory fibres. This assumption may be criticized on two major counts.

1. Evidence is lacking that a stellate ganglionectomy causes a complete degeneration of all the

sympathetic fibres to the extremity, though White *et al.* (1936) and Fatherree *et al.* (1940) are of the opinion that this is predominantly the case. Lewis and Landis (1929-31) showed by the pilomotor response to local faradism that the operation left intact the post-ganglionic fibres to the pilomotor muscles over the lateral aspect of the shoulder and upper part of the arm. That the negative results obtained elsewhere in the extremity can be interpreted as proving the complete absence of post-ganglionic fibres in general and to blood vessels in particular is doubtful and Guttmann's (1940) observations on subjects with excision of the middle and superior cervical ganglia indicate that the area described by Lewis and Landis is only the autonomous zone of supply of the upper ganglia. Foerster, who has observed vasoconstriction in the limb produced by stimulation of the middle cervical ganglion (1935), has also shown that C.6 is distributed to the skin as far as the mid-axial line of the limb (1933). This together with the demonstration by Kuntz (1927) of grey rami from the middle cervical ganglion to C.5 and C.6 and occasionally to C.4 and to C.7 serves as an anatomical basis for the persistence after excision of the stellate ganglion of some post-ganglionic fibres to the limb with a more extensive distribution than that indicated by Lewis and Landis. The density of these persistent fibres is no doubt small but their effect in opposing the vasoconstricting action of local cold may be disproportionately large.

In this connection it may be noted that Grant *et al.* (1931-3) were able to ensure by histological examination that complete degeneration of the sympathetic fibres had occurred, and that Ascroft (1937) found it necessary to excise the middle cervical ganglion as well as the fused first thoracic and inferior cervical ganglia to produce complete degeneration of the post-ganglionic fibres to the upper limbs of monkeys.

2. Another difference that exists between stellate ganglionectomies and peripheral nerve lesions is that in the former the whole of the vascular tree of the limb has been decentralized, while in the latter most of the nervous connections of the main arteries and of the peripheral vascular bed adjacent to the denervated area have been preserved. That this consideration is of importance has been indicated by the observation of Lewis (1929-31a) that vasoconstriction induced in the arteries of the forearm and palm by local cooling inhibits a hyperæmic response in the digits, while Hertzman and Dillon (1940) have shown that the radial artery is subject to vasoconstriction in certain reflex adjustments. Moreover, Lewis and Pickering (1931-3) have alluded to the effect of the temperature of one part of the hand on the temperature and hence on the vessels of adjacent parts. The persistence of a vasoconstricting mechanism in part of the hand and in the proximal vessels would therefore provide opportunities for cooling of denervated digits which are not present in the sympathectomized limb.

There is also a third difference depending on the use of the limb. Lewis and Pickering (1936) have shown that limbs normal except for muscular paralysis tend to be colder than normal. This factor, especially in lesions of more than one nerve, may well play a part in augmenting the causes of vasoconstriction.

Results will be reported in this paper tending to substantiate the objections implied in the above discussion to the deductions of Lewis and Pickering (1936). It will be shown first that it is insufficient for deductive purposes to describe the fingers denervated by lesions of the peripheral nerves as being generally cold, and secondly that the results of peripheral nerve section are not dissimilar to those produced by some stellate ganglionectomies, and that such dissimilarities as do exist are attributable to the extra facilities for cooling in peripheral nerve lesions. Evidence will also be given that the blood flow to denervated digits is adequate to their metabolic needs.

The methods used and the subjects studied are described in paper A.

Results

General Behaviour of the Circulation of Denervated Digits

On questioning patients with lesions of the ulnar or median nerves, they almost invariably state that the affected fingers are persistently cold. cursory examination usually confirms this statement, but fuller investigation shows that no such simple state of affairs exists. This is demonstrated in a series of charts shown in Fig. 1. These were obtained from subject A.E., who incurred an incised wound of the right ulnar nerve in the forearm above the dorsal branch 13 days before coming under observation. At that time he stated that the right fifth finger had been persistently warm since the injury. The finger remained warm till about the 17th day, when it tended to become cold if moved about in

FIG. 1.—Temperature charts of subject A.E. obtained on the days indicated after section of the right ulnar nerve. In this and the succeeding figures the following conventions were used. Abscissæ are time in minutes. Ordinates are temperature in degrees centigrade. Continuous line is the temperature of a denervated digit. Broken line is the temperature of a normal digit. Broken line with dots is the room temperature. Dotted line, when present, is temperature of an additional digit. Lower line of blocks if filled indicates indifferent limbs in water at 18°C., if empty, in water at 44°C. Upper line of blocks if filled indicates extremities under observation in water at 18–20°C., if empty, in water at 38°C. Blocks with oblique hatching show rate of intravenous injection of adrenaline if given.

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cold air, it being first noted when playing billiards in a cool room. At this time it was also found that the finger blood flow was very susceptible to local changes in temperature as seen in Exp. 4 and 5, in which the hands were immersed in water at 38° C. and at 18° C. This state persisted till the 52nd day when the nerve was sutured. Exp. 11 shows the condition 225 days after suture when the only clinical evidence of recovery was a return of the appreciation of heavy pressure to the tip of the little finger. At this time the patient stated that the finger was still persistently cold, but it is clear that some nervous control of vasodilatation and vasoconstriction had returned along with a greater immunity to the effects of local temperature changes.

The course of the vascular changes as described and illustrated in this patient is typical of that of most lesions of the main nerves of the limbs. In the case of sciatic nerve lesions there is little consistency in the statements of the patients in regard to the usual temperature of the toes and not infrequently these are warm when first examined. This, however, is related to the protection of the clothing and no clear distinction can be made between the general behaviour of the circulation of the foot and the hand after lesions of the main nerves.

Through lack of subjects the transition at about the third week from the initial persistent warmth to a tendency to coldness has only been observed in one other patient, but similar experiences have been reported by Lewis and Pickering (1936). These authors were impressed by the coincident loss of the vasodilator axonal reflex, and attempted to correlate the phenomena. However, Freeman *et al.* (1934) have shown in the human, supplementing numerous other investigations on animals, that degenerative section of the sympathetic fibres also leads to an increased responsiveness of the vessels at this time. It is evident, therefore, that the time relations permit the change in circulation to be related to the degeneration of either the sensory or the sympathetic fibres.

It will be noted in Fig. 1 that the behaviour of the circulation of the denervated digits after the third week is errant and is only partially described by the statement that there is a tendency to coldness. In Exps. 5, 7, and 10 there was a vasodilatation when the feet were put in hot water while in Exp. 7 when the feet were put in cold water there was also a vasodilatation. There was, moreover, in addition to a susceptibility to the vasoconstricting action of local cold, also a susceptibility to the vasodilating action of local warmth (Exp. 5 and 7). Thus the circulation of denervated digits is modified both by local changes in temperature and by more remote stimuli applied to the body. These will be considered separately.

Mechanism of the Action of Remote Stimuli

The nature of the problem is indicated by the vagaries of behaviour referred to above. These appear to be due to complex causes for ostensibly

similar stimuli may produce either an increase or a decrease in blood flow and the time relations to the stimulus are variable, the reaction occurring sometimes immediately and at other times not for 15 to 20 minutes. Both phases of this double type of response are seen in Fig. 1, Exp. 7. Here immersion of the feet in hot water produced an immediate increase in blood flow, which was followed 20 minutes later by a further increase coincident with the reflex vasodilatation in the normally innervated fingers.

In the course of these experiments it was found necessary, if it was desired to maintain a fairly high blood flow in the denervated digit in the presence of a low room temperature, to have the subject warm. It may be noted that Lewis and Pickering (1936) did not make this observation, so failed to find that denervated digits could stay warm. The experiments charted in Fig. 2 illustrate some of the results bearing on this point. In subjects J.M., J.B., and L.S. (Exp. 2), it was found that immersion of the extremities in water at 38° C. for 5–10 minutes did not result in a stable state of vasodilatation until the subjects were warm as indicated by vasodilatation in the normally innervated digits. In subjects S.R., N.R., A.I., and R.B., vasodilatation did persist in the cold state, but this was increased after the feet were put in hot water. Subject L.R., was an exception in that maximal vasodilatation was produced when cold, but he was also exceptional in having a lesion of both ulnar and median nerves. The reverse phenomenon, that is a vasoconstriction when the body is cooled, was observed in subjects J.M., J.B., N.R., L.R., and L.S. (Exps. 1 and 2). Subject A.K., was almost unique in the failure of the combination of local and general warmth to produce a lasting vasodilatation. It is of interest to note that Grant (1935) found in his large series of rabbits with sympathectomized ears several similar examples of failure to maintain a vasodilatation after local warming. The explanation is not apparent.

These experiments lent themselves to the interpretation that the state of the remainder of the circulation of the limb had a definite influence on that of the denervated digit and was probably instrumental in producing some of the remote effects now under consideration.

It was thought that cases with lesions involving the nerve supply of the limbs to different degrees might furnish material to support this supposition. In Fig. 2 (Subject A.I.) is shown the temperature record obtained from a patient suffering from denervation of a single digit, in Fig. 3 records from subject L.H., with denervation of the whole hand, and in Fig. 4 records from subject S.B., with denervation of the whole arm. In subject A.I. marked consensual responses were present and these also occurred in lesser degree in subject L.H. Subject S.B. showed only the slightest indication of such responses. This evidence while corroborative is far from satisfactory because of the great individual differences that have been encountered

FIG. 2.—Temperature charts of different subjects. Conventions as in Fig. 1. In the experiments on subjects L. R. and S. R. severe pain was induced at the times indicated by strong faradism applied to the legs for 1 min.

in apparently similar cases and also because somewhat similar responses have been encountered in sympathectomized limbs. Moreover, this conclusion that the intact vasomotor innervation of the limbs influences the circulation in the denervated digits is open to the objection that evidence of such an influence was lacking in subject A.E. during the first two weeks following the nerve lesion (Fig. 1, Exps. 1 and 2). The appearance of responses in the denervated finger at the same time as denervation

sensitivity is beginning to be manifest suggests that they may be due to hormonal influences. It may also be noted that not all the phenomena are explained by the vasomotor hypothesis, as, for instance, when the feet are immersed in hot water the immediate vasodilatation produced in the denervated digit usually has no counterpart in the normally innervated digits.

This suggests the necessity to hypothecate an hormonal factor. Also supporting the hormonal

explanation of some of these changes in the circulation of denervated digits is the vasoconstriction caused by severe pain (Fig. 2, subjects S.R. and L.R.), which is much more prolonged than in the normal digits and resembles the response to intravenous adrenaline (Fig. 2, subject L.S. (Exp. 2)).

It was also thought possible that some of these changes might be explicable on the basis of the liberation of a histamine-like substance from the limbs immersed in hot water. Lewis and Pickering (1936) have shown that the vessels of denervated digits are readily affected by histamine, while Tinel and Ungar (1935) consider that immersion

cutaneously on another occasion caused in 30 minutes a marked secretion of H.Cl. It was concluded that immersion of the limbs in hot water as practised in this investigation did not cause a significant rise in the concentration of histamine-like substances in the blood and that this was probably not the cause of the variations in digital blood flow.

To determine whether the hormonal or the vaso-motor explanation of the changes in circulation was correct the following case was available. Subject S.W. had a clinically complete lesion of the right median nerve of 20 years' standing and also a circulatory disorder of the same hand of 9 months'

FIG. 3.—Temperature charts of subject L.H. Conventions as in Fig. 1. Systolic B.P. obtained from L.F.3.

of a cat's foot in water at 50° C. for 2 min. released histamine. Evidence on this point was obtained by the approach of Kalk (1929), who demonstrated the release of such a substance in cases of urticaria factitia, using the gastric mucosa as indicator. Accordingly a fasting normal subject was intubated and the gastric contents were aspirated at 10-minute intervals for 90 minutes. At 20 minutes the legs were immersed in water at 46° C. for 30 minutes. This was very painful and caused a marked tender erythema. No free H.Cl. was secreted throughout the period. Histamine phosphate 0.5 c.c. of a 1-1,000 solution given sub-

duration following exposure to cold. He stated that for the past 20 years the right 2nd and 3rd digits had been colder than the rest of the hand, but his immediate disability was swelling and stiffness of the whole hand when exposed to cold. So far as could be ascertained the denervated fingers were affected in a similar manner to the others. A preganglionic sympathectomy was performed with complete relief of these complaints. In Fig. 5 are illustrated some of the results obtained before operation (Exps. 1, 2, 3, and 4), three weeks after operation (Exps. 5, 6, 7, and 8) and 6 months after operation (Exps. 9, 10, and 11).

FIG. 4.—Temperature charts of subject S.B. Conventions as in Fig. 1.

FIG. 5.—Temperature charts of subject S.W. Conventions as in Fig. 1. Systolic B.P. from R.F.4.

Exps. 1 and 2 show that vasomotor reactions were normal in the digits not affected by the median nerve lesion, while the right index finger behaved in a manner typical of a denervated digit, that is, it tended to be cold until warmed and then remained warm. It also responded to remote influences undergoing a vasoconstriction when the feet were put into cold water. Exp. 3 shows that R.F.2 was hypersensitive to adrenaline compared to R.F.5 and L.F.2 both of which had the same sensitivity. Exp. 4 is included to show the effect of block of the right stellate ganglion which caused a satisfactory rise in blood flow in the 5th digit, but had no effect on the 2nd digit. This lack of effect is of little significance considering the initial cold state of the finger which would offset any tendency to vasodilatation. Exps. 5, 6, and 7 done three weeks after preganglionectomy show by the high constant temperature of R.F.5 that all the vasomotor fibres had been completely interrupted. The 2nd digit, however, showed in comparison to the pre-operative state a diminished circulation

and a greater tendency to cooling, which was only combatted by keeping the room temperature above 22° C. These experiments also show that putting the feet in cold water either checked the fall in temperature of the finger or caused it to rise. Unfortunately no blood pressures were taken, but from analogy to those recorded in Exp. 9, it seems that the changes in finger temperature might have been due to variations in blood pressure. The poor maintenance of an increased blood flow at this time was probably associated with the general debilitated state of the patient. He was apyrexial, but felt "knocked about" by the operation. The evidence does not permit a judgment as to whether this decreased flow was caused by a low blood pressure, to the circulation of some vasoconstricting agent, or to some change in the tissue metabolism, but it is to be noted that once more Grant (1935) has encountered the same phenomenon in sympathectomized rabbit's ears in similar circumstances.

Six months after operation the patient was very fit and reported that the whole of the right hand

was persistently warmer than the left although exposed to all the trials of a hand of a dispatch rider in the winter. Exps. 9, 10, and 11 demonstrate the truth of this statement and substantiate the observations of Atlas (1941) on a somewhat similar case. These experiments indicate that a persistently high blood flow was now the usual condition in the index finger and that even after immersion of the hands in water at 18° C. for 10 minutes the denervated finger tended to become warm. This is a striking contrast to the behaviour not only of the same finger before operation, but also to that of most of the other denervated digits which have been examined. This difference must be ascribed to the section of the vasomotor nerves to the limb and therefore confirms the assumption made above that the intact vasomotor nerves in cases with peripheral nerve lesions influence the circulation of the denervated digits.

There is, however, good evidence in Fig. 5, Exp. 9, that hormonal influences also play a part in causing variations in the circulation. The definite vaso-

sensitivity to adrenaline now existed in the little finger and only a slight indication of this was found in the index (Fig. 6, Exp. 2). These results were interpreted as indicating that the operation had produced a preganglionic sympathectomy of the index and a ganglionic sympathectomy of the little finger. The anatomical basis for this conclusion has been referred to in the introductory discussion.

Two other inferences may be drawn from this case.

(1) The similarity of the circulatory status of the post-ganglionectomized digit having intact afferent fibres (subject S.S.) and of that of the completely denervated digit (subject S.W.), both limbs having the remainder of their vasomotor innervation decentralized, indicates that the presence of intact afferent fibres is of little consequence to the digital circulation under the conditions of these experiments.

(2) The variations in blood flow in a sensitized digit of a sympathectomized limb indicate an hormonal causation of these changes. It is presumed that this hormone is adrenaline and further evidence on this point is given in paper E.

FIG. 6.—Temperature charts of subject S.S. Conventions as in Fig. 1, except that continuous line represents a sympathectomized digit.

constriction occurring particularly in R.F.2 in the face of a raised blood pressure while the feet were in cold water can only be due to a change in the composition of the blood. It may be noted that the prompt relaxation of this constriction when the feet were returned to hot water rules out the possibility that these changes were caused by variations in blood temperature.

It is of interest to compare the records of subject S.W., Fig. 5, with those of subject S.S., Fig. 6, in whom a stellate ganglionectomy was performed for mild Raynaud's disease, which affected equally all the digits of both hands with the exception of the thumbs. Exp. 1 shows that before operation no abnormality was demonstrated in the responses to warming the body, immersion of the hands in cold water nor to the injection of adrenaline. Three months after operation the right index finger was persistently warm, but the little finger was hypersensitive to the local vasoconstricting action of cool water and also showed a slight vasodilatation when the feet were put in hot water and a vasoconstriction when taken out of hot water (Fig. 6, Exp. 3). It was also possible to show that a hyper-

The influence of blood pressure changes on the blood flow of denervated digits has been referred to above. In Fig. 3 and in Fig. 5, Exp. 9, are plotted the systolic blood pressure changes associated with immersion of the feet in hot and cold water, as recorded from the digital arteries. Little reflexion of these changes is seen in the finger temperatures, except the transitory rise in the blood flow to R.F.2 in Fig. 5, Exp. 9. It has been shown previously, that a marked rise in digital blood pressure is caused by a peripheral vasoconstriction (Doupe *et al.*, 1939). In hands that have lost only a part of their vasomotor fibres, i.e. ulnar or median nerve injuries, the changes in blood pressure might be expected therefore to be greater than those reported here and might well account for the variations in finger temperature not otherwise explained. These are usually minor in degree (Fig. 1, Exp. 1), but on occasion major changes in blood flow seem to be determined by this factor. Thus in Fig. 1, Exp. 7, and in Fig. 2, subject T.B., the terminal rise in temperature of the denervated finger may well have been due to a rise in blood pressure shifting the balance in favour of vasodilatation. There is a

possibility that some of the phenomena here ascribed to a rise in blood pressure may be due to the release of a vasodilating agent, as the work of Bender (1938) has shown that a cholinergic substance may at times be present in the circulation.

Plethysmographic records have substantiated these findings so far as hormonal and blood pressure effects are concerned, but they provide no clear evidence of the remote influence of vasomotor nerves.

S.R., while in the three successive experiments on subject L.H., Fig. 3, vasodilatation occurred more readily the higher the room temperature. In Fig. 7 are shown the results obtained from a subject (C.B.) with a sciatic nerve lesion who showed a rather exceptional tendency to vasoconstriction. The denervated toe failed to maintain a vasodilatation at a room temperature of 16° C., and the fall of toe temperature was not interrupted by body warming. However, a gradual rise of room temperature from

FIG. 7.—Temperature charts of subject C.B. Conventions as in Fig. 1.

In the foregoing, illustrations of the reactions of the circulation of denervated digits in response to cooling and warming the body and to other stimuli have been given. These have been explained as being due to (a) the action of vasomotor fibres still supplying the limb; (b) variations in the amount of circulating adrenaline; and (c) variation in local and general blood pressure. In cases with only part of the limb denervated no precise distinction between the effects of vasomotor and hormonal influences has been possible.

Effect of Local Temperature on Blood Flow

Evidence indicative of the vasoconstricting effect of low room temperatures is given in Fig. 2, subject

18° to 23° C., produced at about 22° C. a vasodilatation in the denervated toe. It has also been shown above that if the remainder of the blood vessels of the limb be in a state of vasodilatation either through reflex inhibition of constriction (Fig. 2, J.B.) or by severance of all the sympathetic nerves as in a brachial plexus lesion (Fig. 4) the digital vessels will resist even the vasoconstricting influence of a room temperature of 14° C. This behaviour, reminiscent of that of sympathectomized limbs, suggested that a further experimental comparison should be made of the effects of local temperature changes on the circulation of denervated and sympathectomized digits.

Reference may be made to Fig. 5, Exp. 11, to

FIG. 8.—Temperature charts of different subjects. Conventions as in Fig. 1, except that in the case of C.S. and J.R. the continuous line represents a sympathectomized digit and in C.S. the broken line also represents a sympathectomized digit. Cross hatched block indicates time of immersion of limbs in water at 6° C.

show that immersion of the hand in water at 18° C. for ten minutes produced a vasoconstriction in a digit with a peripheral nerve lesion but had little effect, as judged by the prompt warming, on the finger with a preganglionic sympathectomy. Fig. 8 shows that similar immersion of the foot did not cause a vasoconstriction in the preganglionectomized lower extremity (subject C.S.) while it did produce a vasoconstriction in the completely denervated foot (subject R.W.). Experiments 1 and 2 on subject J.R. (Fig. 8) show that in a limb, normal except for a stellate ganglionectomy done three months before, such immersion produced a vasoconstriction which tended to persist, similar to that in digits with a complete denervation. It is concluded therefore that complete denervation and sympathetic degeneration

absence of response is not due to the cold sensitive state of the denervated vessels has been shown by Lewis and Pickering (1936) and is further supported by observations on subject S.S., who as a result of a stellate ganglionectomy was left with the little finger hypersensitive to the vasoconstricting action of cold and the index not hypersensitive (see Fig. 6, Exp. 3). In Fig. 9, subject S.S., it is apparent that the vasodilator responses in these digits were similar, and further that the same type of phasic vasodilatation occurred in response to extreme heat. This phasic response to extreme heat is present in the normal fingers, but is difficult to demonstrate. It is absent from the denervated digits (subject A.I.). It should be noted that the site at which the digital temperatures were taken was insulated from the

FIG. 9.—Temperature charts of different subjects. Conventions as in Fig. 1, except that in S.S. continuous line represents a sympathectomized digit. Hands in rubber gloves and distal two phalanges immersed in water bath the temperature of which is indicated by a heavy continuous line.

tion produce a similar hypersensitive state in the digital vessels to the vasoconstricting action of moderate cold.

This similarity between the effects of a peripheral nerve lesion and sympathetic ganglionectomy does not hold for low temperatures. Thus in Fig. 8, subject J.R., Exp. 2, immersion of a ganglionectomized hand in water at 6° C. for five minutes produced a vasodilatation, while fifteen minutes at 6° C. had no vasodilator effect on a completely denervated foot (subject R.W.).

Further examples of this difference in reaction to low temperatures, which was described by Lewis (1929–31b), are given in Fig. 9, subject S.R., which shows the absence of a response to water at 0° C. of a denervated digit while a response was present in a normal digit of the same hand. That this

heat more effectively than the remainder of the digit, and so no deduction is possible as to the temperature at which the phasic response is initiated. Lewis and Love (1926) have shown that axonal vasodilatation first appears when the surface temperature is kept at 43–44° C. and the present observations are consistent with this figure.

In order to determine the temperature range over which the sympathectomized and the denervated digits react similarly a series of blood flow determinations were made while the temperature of the water in the plethysmograph was lowered. For this purpose subject J.R., with a right stellate ganglionectomy of six months' duration but an otherwise normal limb, was compared to subject L.R., with a lesion of the ulnar and median nerves in the upper arm and subject S.B., with a complete

brachial plexus lesion. Blood flow was measured with the hand in a water plethysmograph and the temperature of the index finger was taken by a thermocouple placed under a rubber finger stall. The temperature of the water was lowered in steps, 20–30 minutes being allowed after each change to

on subject S.B., and it will be noted that no increase of flow occurred at low temperatures nor did a difference in finger and water temperature develop. In Fig. 12 it will be seen that in all three subjects the blood flow reached a minimum at about 16–18° C. By lowering the temperature still further

FIGS. 10 and 11.—Plethysmographic records ($\times \frac{1}{4}$) of subjects J.R. and S.B. showing rate of increase of hand volume at different bath temperatures when venous outflow was impeded by a cuff on the wrist. The temperatures of the tip of the index finger and of the water bath have been inserted. Time in 1-sec. and 10-sec. intervals.

permit an equilibrium to be established, as indicated by a steady finger temperature. Fig. 10 shows typical blood flow curves on subject J.R. The actual estimations of blood flow at the faster rate were made on paper travelling at 10 times the speed of that shown. It will be noted that the divergence of the finger temperature and the water temperature was large at intermediate temperatures and again at low temperatures. Fig. 11 shows similar curves

no change occurred in the completely denervated hand (S.B.), a very slight rise occurred in the hand with innervation of the thumb area (L.R.), while a large rise occurred in the ganglionectomized hand with the afferent fibres intact (J.R.).

This method of investigation was adopted from Freeman (1935) who, in a study of human stellate ganglionectomies, obtained similar results at temperatures above 20° C., while Freeman and Zeller

FIG. 12.—Chart of measurements of blood of the hands of 3 subjects at different temperatures. Units indicated on the face of the graph.

(1937) extended the observations on dogs, noting that below a temperature of 14° C. evidence of injury occurred. In restricting their procedures to temperatures above this they found that a limb with a chronic sciatic nerve lesion in addition to a sympathectomy behaved in a manner similar to those with only a sympathectomy.

It is apparent that the above results are all consistent in indicating that at tissue temperatures above 16–18° C. the presence or absence of vasodilator axonal reflexes is immaterial to the circulation, while at temperatures below this the presence of such reflexes increases the circulation. This conclusion is also consistent with the observations of Lewis (1929–31) who found no clear evidence that the vasodilator reflex was activated at temperatures above 15° C., though occasionally such a

in the affected digits. Examination of such patients shows that to some extent this is a subjective observation as the finger may be as warm as the others, though they still describe it as feeling cold. In such cases Lewis and Pickering (1936) noted that there was some delay in warming of the fingers after immersion in water at 7° C., despite the presence of normal axonal vasodilatation, and were unable to reconcile the observations with their hypothesis.

Three subjects have been tested in this series. Subject A.E. (Fig. 1), 225 days after suture of the ulnar nerve showed a delayed response to warming and cooling the body. Subject H.J. (Fig. 13) with an incomplete lesion of the left ulnar nerve from an old-standing valgus deformity of the elbow showed a definite tendency of the affected 5th finger to be colder than the others, and, as might be expected,

FIG. 13.—Temperature charts of subjects H.J. and A.L. Conventions as in Fig. 1, except continuous lines represent incompletely denervated digits.

response was noted at 18° C. Therefore, before these reflexes are activated the tissues must be cooled to this degree. It is obvious that if a limb remains persistently warm, as is the common state of sympathectomized limbs, it is not due to the presence of these reflexes. It is also obvious that if a digit remains at a temperature at 17 to 20° C., as is the common state of denervated digits (Fig. 2), it is not due to the absence of these reflexes.

The experiments so far reported show, under the controlled conditions of the laboratory in which the limbs are kept motionless and a similar exposure to the air maintained, that the totally denervated digits are similar in their vascular reactions to digits with degeneration of their sympathetic fibres, provided only that they are not cooled beyond 15° C. Denervated digits are, however, depending on the extent of the denervation, influenced directly or indirectly by the intact vasoconstrictor innervation of the limb and so are more subject to the cooling power of the environment. Under conditions of daily life other factors, such as disuse, as described by Lewis and Pickering (1936) and the lack of appreciation of cold and of the consequent active measures to combat it afford additional reasons for the greater tendency of denervated digits to be cold.

Incomplete Nerve Lesion

Subjects with incomplete nerve lesions or during the stage of recovery usually complain of coldness

this was most noticeable when the normal fingers were at intermediate temperatures (Fig. 13, Exp. 1). In the same experiment the affected finger showed a slight sensitivity to the vasoconstricting action of local cold, while in Exp. 2 it showed some hypersensitivity to adrenaline. In subject A.L. (Fig. 13) the observations were made two years after suture of the ulnar nerve in the mid forearm. At this time patchy sweating was present on the fifth finger and pressure pain was present in the tip of the digit. An increased sensitivity to adrenaline was demonstrated but otherwise no obvious abnormality was found except a slight defect in neurogenic vasoconstriction. This subject, however, was not examined in the state of partial vasodilatation.

The above observations indicate that in subjects with partial sympathetic innervation of their digital vessels a hypersensitivity to moderate cold and to adrenaline may be present. This produces some retardation of vasodilatation and when the sympathetic vasoconstrictor fibres are in a state of intermediate tone the affected fingers are likely to be colder than those digits which have a normal innervation.

Reactive Hyperæmia

Lewis and Grant (1924) have shown by noticing the flush following release of arterial occlusion that reactive hyperæmia occurs in digits denervated by peripheral nerve section. Goldblatt (1926) has

shown in animals that the response is independent of the nervous system, while Grant and Bland (1929–31) have indicated that arteriovenous anastomoses are among the vessels involved in the dilatation.

Examples of these truths have been readily obtained. Two subjects S.W. and A.K. were chosen in whom unique difficulty was experienced in inducing a steady state of vasodilatation in the denervated digits. Fig. 14 shows an absence of response to 30 min. arterial occlusion of the digital circulation if the digits were maintained at 18° C. for this period. However, when the hands were immersed in water at 38° C. for 15 minutes and then, so as to permit comparison with the previous response, immersed in water at 18° C. for 10 minutes and for a further 5 minutes exposed to the air, release of the cuff caused a striking increase in the temperature of the denervated digits. The rapidity of this increase indicated a rate of blood flow so high as to be only explicable on the basis of a

are quoted by Grant (1935), but he failed to find any alteration in the histology of denervated vessels of the rabbit's ear.

Substantiation of Grant's results were obtained in subject A.H. with a sciatic nerve lesion who, because of intractable ulcers, required amputation below the knee. The dorsalis pedis, the posterior tibial, and the digital arteries of the great toe appeared histologically to be normal in every respect.

Discussion

In the presentation of the above results their bearing on causation of the usually diminished circulation of denervated digits was discussed and it was concluded that so long as their temperature did not fall below 16 or 17° C. the sensitization to cold produced by degeneration of the sympathetic fibres was the major cause of the phenomenon. This sensitization to cold was made the more manifest by the action of adrenaline, the action of the intact vasomotor nerves to the limb and by disuse.

FIG. 14.—Temperature charts of subjects S.W. and A.K. to show the effect of temperature on reactive hyperæmia. Conventions as in Fig. 1. Cuffs on the proximal phalanges of the digits inflated to 200 mm. Hg. for the periods indicated on the chart.

dilatation of the arteriovenous anastomoses. This increase was in contrast to the absence of any change in the normally innervated digits and was comparable to that occurring in the preganglionectomized digit (subject S.W.) except that here the rise was maintained. In this instance it was also noted that sensation returned to the preganglionectomized digit (R.F.5) within two minutes and to the normal digit (L.F.2) in five minutes.

It is apparent, therefore, that reactive hyperæmia: (1) is not dependent on any nervous mechanism; (2) is greatly slowed by a high sympathetic vasoconstrictor tone; (3) is not affected by the vasoconstriction caused by cooling the denervated digit; (4) is, in the denervated digit, mediated in part by the arteriovenous anastomoses.

Histology of Arteries

The literature is not lacking in descriptions of the pathological effects of nerve lesions on the arterial wall (Todd 1913, Stopford, 1918). Other references

The different effects of preganglionectomy, ganglionectomy, and peripheral nerve section on the circulation have been indicated. The finding that stellate-ganglionectomy need not produce complete degeneration of the post-ganglionic fibres, together with the demonstration by Kuntz (1927) of the variable distribution of fibres from the middle cervical ganglion, suggests an explanation for some of the better results following this operation. It seems probable that even a very partial preservation of the post-ganglionic fibres would confer a relative immunity on some of the vessels to the effects of local cold. A persisting high blood flow in these vessels could then combat the cooling of the tissues with the result that even the fully sensitized vessels would dilate and give the appearances typical of a preganglionectomy. It should be noted, however, that de Takats (1940) practises excision of both stellate and mid-cervical ganglia and claims good results.

The tendency to vasoconstriction shown by

denervated digits suggests a resemblance to Raynaud's syndrome, and Grant (1935) has wondered if involvement of the nerves may play a part in the pathogenesis of this condition. Several points argue strongly against this theory. Fatherree and Allen (1938) have shown that patients with Raynaud's syndrome have no hypersensitivity to adrenaline. Conversely, subjects with partial lesions of peripheral nerves in the present series have not been observed to have Raynaud's syndrome, and direct questioning has not, in a large series of cases, elicited a history suggestive of vasospasm. However, in the variety of Raynaud's syndrome occurring in workers with pneumatic tools it seemed not impossible that there might be some injury to the nerve fibres. Subject S.S. was a mild case of this sort but no abnormality in the response to adrenaline could be demonstrated. Denervated fingers not uncommonly exhibit a slight cyanosis compared to the other digits, but this is never so intense as that seen in Raynaud's syndrome. Moreover, in Raynaud's syndrome the essential defect is a vascular spasm which the tissue metabolites are unable to relax. This defect is not present in peripheral nerve lesions as shown by the ready response to reactive hyperæmia despite thorough cooling of the digits which would ordinarily cause in them a pronounced vasoconstriction. This would indicate that in peripheral nerve lesions the blood flow is adequate to the needs of the tissue, while in Raynaud's syndrome ischæmia occurs.

Under the term trophic changes may be included the diminished nail growth, loss of finger pulp, and thinning of the skin. These have been well depicted by Lewis and Pickering (1936) who ascribed them to an habitual coldness and to a deficient blood supply by analogy with similar changes occurring in Raynaud's syndrome. As it has been shown above that there is no reason to believe that the blood supply to denervated digits is deficient for the needs of the tissue, these changes may be ascribed simply to the diminished growth and metabolic activity consequent on the low temperature. Evidence is given in paper G that similar changes do not occur in the proximal parts of the limbs following denervation and here the effect on the skin temperature is minimal. Crucial evidence as to whether these digital changes are in any sense neuro-trophic might be obtained from the observation of cases in semi-tropical climates where it is likely that denervated digits would usually be warm.

Lewis and Pickering also ascribe to a deficient blood supply the intractable healing of ulcers and the occurrence of chilblains. No evidence of the former was found (see paper C). The incidence of chilblains must be very low in denervated digits. Thus in a personally observed series of 62 median nerve lesions, 25 of which were complete, 81 ulnar nerve lesions 32 of which were complete and 16 sciatic nerve lesions 6 of which were complete, no case with chilblains was found.

There now remains to be considered the nature of cold sensitivity. It is usually considered that

cold acting directly on the contractile elements of the blood vessels is the cause of vasoconstriction. Certainly the observation of Lewis and Landis (1929-31) that warming immediately increased the pulsation of digital arteries that had been sympathectomized and the tendency of excised arteries to go into spasm when cooled as shown by Kesson (1912) favours this view. Experiments with other types of smooth muscle, the iris (Verbitzky, 1923), and the stomach (Singh, 1940), however, showed that the tone relaxed at temperatures below 25 to 30° C., and a similar reaction has been found in mesenteric arteries (Cruikshank and Rau, 1927). An alternative explanation is provided by the conclusions of Lewis (1927) indicating that the reduction in blood flow to the skin at reduced temperatures is secondary to a reduction in tissue metabolites. In favour of this suggestion is the finding of Freeman and Zeller (1937) that O₂ usage and blood flow are affected in a parallel manner by changes in temperature. It would appear that the theory of Bazett and McGlone (1928) attributing the vascular effect to changes in pH reconciles these two points of view. A fall of temperature would directly raise the pH and this would produce vasoconstriction as shown by Kurtz and Leake (1927). At the same time the lowered temperature would decrease the formation of acid metabolites and so indirectly lead to an elevation of pH and vasoconstriction.

These local influences plus the increased reactivity of the denervated blood vessels would appear to offer sufficient explanation for the much-debated phenomenon of regain of tone following sympathectomy. In particular there seems to be no need to hypothecate a circulating vasoconstrictor substance as has been done by Grant (1935). At the same time there is evidence in patients (subject S.W.) and in animals (Grant, 1935, Ascroft, 1937) that systematic disorders tend to induce vasoconstriction. This influence must be mediated by hæmatogeneous factors, but it is an open question whether these directly influence the vessels or the metabolism of the tissues. Perhaps in favour of the latter view is the fact that systemic disorders leave their traces on growing tissues, such as the nails, and on bones and teeth in children.

Summary

Observations on subjects with preganglionic and ganglionic sympathectomies and patients with peripheral nerve lesions have been reported.

The digital vascular reactions in peripheral nerve lesions are similar to those following sympathetic ganglionectomies. These observations bring the results on humans into agreement with those on other mammalia.

The tendency to coldness of completely denervated digits is due to the hypersensitivity to the local vasoconstricting action of cold caused by the degeneration of the sympathetic fibres. This action of cold is made apparent in denervated digits because of the facilities for heat loss afforded by vasoconstriction in the remainder of the limb, the

action of adrenaline, and the cooling caused by disuse.

Part of the difference in the habitual states of denervated digits and ganglionectomized digits has been ascribed to the persistence in the latter of some post-ganglionic fibres.

It was concluded from observations on reactive hyperæmia that the blood flow to denervated digits is adequate to the needs of the tissues.

The digital atrophy was ascribed to the lowered tissue metabolism consequent on the usual coldness.

The relationship of Raynaud's syndrome to denervation sensitivity has been discussed and no correlation made.

The effect of temperature on the vessels has been discussed and its relationship to changes of pH and of tissue metabolism has been considered.

The regain of tone following denervation has been ascribed to the action of local influences on sensitized vessels. No necessity was found to assume the presence of a hæmatogenous factor except in the circumstance of systemic disorders.

Since the completion of this paper Richards (1943), has reported observations covering somewhat the same ground.

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