STUDIES OF TISSUE MAINTENANCE

III. PERSISTING BLOODLESSNESS AFTER FUNCTIONAL ISCHEMIA

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When the circulation reenters a part that has been briefly deprived of blood there ordinarily develops in it an active hyperemia, as every student of vascular physiology knows. But if the deprivation has endured for a somewhat longer time the happening is diametrically different. As the present paper will show, an obdurate local vasoconstriction has in some way been invoked, one so effective that the tissue involved remains closed off from the circulation for a greater or less period even though the flow through neighboring regions of the same sort is unusually good and the systemic blood pressure above the original level.

Persisting ischemia of the sort here described can readily be demonstrated with the aid of highly diffusible vital dyes, in animals with blood bulk reduced by bleeding or by solutions inducing anhydremia. Under such circumstances a patchy ischemia of the superficial tissues develops after some minutes, one so complete that the patches become pronouncedly acidotic, and even highly diffusible vital stains (phenol red, brom phenol blue, Patent Blue V) fail to enter them (I). If the blood bulk be restored soon after these patches have developed they rapidly disappear; but when they have endured for a little while the restoration has merely the effect of accentuating them through the passage of additional stain into their surroundings, and an hour or more may elapse before, by a gradual coloration, they are lost in the general hue.

Experiment 1.—With barium sulphide the hair was carefully removed from the body and thighs of a well nourished and vigorous, white female cat. No cutaneous inflammation ensued during the next few days. The animal was kept in a well-warmed room. For twenty-four hours prior to operation it was given no food,
but was allowed water. Under ether the trachea was cannulated with a Y tube for the purposes of anesthesia; the right carotid was connected with a mercury manometer for blood pressure readings; and the left axillary artery and a vein of the left foreleg (radial branch of the cubital) were cannulated, for bleeding and the injection of solutions respectively. All this took 9 minutes. The cat was then laid upon its back on an electrically warmed pad. The limbs assumed natural positions. The carotid blood pressure was constant at 142 mm. Hg.

Now 30 cc. of blood was taken from the axillary artery in the course of 3 minutes 15 seconds, and 16 minutes later 17 cc. more (in 3 minutes), and after the lapse of another 10½ minutes 8 cc. more (in 2 minutes). In this way the carotid blood pressure was reduced to 74 mm. 31 minutes from the beginning of the depletion an injection of phenol red was made. The cat weighed 2240 gm. and the warmed 4 per cent dye solution (at pH 7.4 and isotonic with the blood) was given in the ordinary proportion of 3½ cc. per kilo, 8.25 cc. being gradually run into the vein during 80 seconds. After the injection the pressure did not improve, but tended to fall as in other animals bled to the limit and injected only with fluid which would not remain in the vessels. Three minutes later, when the pressure was only 60 but the breathing good, the lips, gums, and conjunctivae had become deep red, with an orange cast suggestive of acidosis, whereas the trunk and thighs showed merely a few orange patches widely separated by pallid unstained regions. By this time a normal cat would have been brilliantly red.

The blood, as taken, had been defibrinated with care so that as little as possible should be lost. It was now aerated, warmed and restored to the animal by successive injections. A mere 4½ cc., given 3 minutes after the dye was all in, brought the pressure to 110 millimeters and 15 cc. 10 minutes later carried it to 150, that is to say above the initial level. Despite this recovery the staining scarcely progressed; and two further injections of all the remaining blood (22 cc. in 1 minute 45 seconds and 9½ cc. in 35 seconds) were made 18 and 20 minutes respectively after the dye injection. The carotid pressure reached 160 and remained at that figure for the next three quarters of an hour. The heart beat violently and the arterial pulsations were accentuated. After the return of the blood the deeply stained conjunctivae, gums and lips practically at once became red without trace of orange—between jasper red and eugenia red (Ridgway) (2)—showing that the slight general acidosis had disappeared. Over the trunk and thighs, however, the changes were very gradual. Large areas were still unstained 3 minutes after the final blood injection, and where the dye penetrated it had a hue between ochraceous orange and ochraceous buff. Little by little the coloration extended, but even after half an hour there were still many unstained patches such as are ordinarily associated with a diminished blood bulk (3). The areas to which the phthalein had originally been distributed were now turning red whereas those into which it penetrated later were orange. These various local differences caused the body surface to appear piebald with orange, red and white. Forty-six minutes after the last return of blood there were no longer any unstained areas but a pronounced
spotting of pale orange upon red persisted. The orange patches were now small, only \( \frac{1}{2} \) to 1 cm. in diameter.

To hasten the disappearance of the patches 40 cc. of warm Ringer’s solution was injected intravenously 47 minutes after the last return of blood. The injection took 2 minutes. The blood pressure, which had been at 158, fell transiently but recovered to 152. Within the next twenty minutes all the orange spots disappeared.

In this experiment the patchy ischemia induced by the bleedings lasted at least half an hour after the blood had been restored and very probably for more than an hour, if one can judge from the persistence of areas of local acidosis that had been slowly colored by diffusion inwards from the well-stained tissue round about. The preliminary bleedings had been done gradually and at intervals, in order to allow opportunity for readjustments within the organism, and more especially for the passage of fluid out of the tissues into the vessels to make up the blood bulk. As Starling has shown (4), compensatory changes of the latter sort are practically at an end within 5 minutes after a single brisk bleeding, and subsequent bleedings do not elicit them in any important degree. The depletion was pushed very nearly to the limit, as indicated by the tendency of the blood pressure to fall after it had been accomplished, despite the introduction of dye dissolved in a salt solution. The inability of salt solutions to restore the blood pressure on such extreme occasions is well recognized. Only 51 cc. of blood was returned as compared with 54 cc. taken, but the said 54 cc., as drawn from the vessels, consisted in part of tissue fluid; for, as is well known, the last blood removed at even a rapid bleeding is dilute as compared with the first. It follows that the actual quantity of blood taken was less than our figure would indicate. The circulatory state after the reinjection supports this view. It was one of evident plethora, the heart beating violently, the pulsation of the arteries unusually prominent, and the veins engorged.

The quantity of phenol red injected into the depleted animal was not reduced from that which would have stained a normal cat evenly and deeply. The blood bulk, though, had been reduced by nearly half at the time of the dye injection. The question comes up of whether under such conditions the persistent patching may not have been caused by an untoward influence of the dye. True, previous experi-
ment had repeatedly shown that an acidotic patching indicative of local ischemia develops when the vital staining precedes the bleeding (5), which last removes much of the dye still in circulation. But this does not mean that the patches would have persisted had the blood been restored to the body. To determine what influence, if any, the dye had in the persistence of the patching was not difficult.

Experiment 2.—A vigorous, male, white cat of 2240 gm. was prepared like that of Experiment 1, save that it was fasted for only 16 hours prior to operation. The same cannulations were performed, under ether, in 19 minutes. The carotid blood pressure was found to vary between 140 and 145 mm. of mercury. A bleeding of 38 cc. in 120 seconds was now carried out, and others followed of 12 cc. in 70 seconds, 15½ cc. in 90 seconds and 6 cc. in 45 seconds, 14½, 23½ and 51½ minutes respectively from the beginning of the first. The carotid pressure was in this way brought down gradually to 84 mm. Hg. The body surface had become notably pallid, with suggestions of even paler blotches here and there. The animal was still in excellent condition, stirring under the light ether. The blood pressure tended to fall after the last bleeding. It decreased to 74 mm. Hg in a period of 9 minutes, when the reinjection of blood was begun, the animal being in good condition at this time. Less than 2 cc. had been lost in defibrination but 8.4 cc. more was withheld, since the intention was to throw that much phenol red solution into the circulation, and the avoidance of a sudden plethora seemed desirable. All the rest of the blood, aerated and warmed, was introduced by way of a foreleg vein in the course of three minutes, and was followed immediately by the 4 per cent phenol red solution (during 65 seconds). The blood pressure rose to 148 and fell again slowly to 130. The tip of the nose and the gums became red but the superficies of the trunk and thighs colored very slowly, and where the phthalein entered it was at first orange, not red. Large patches remained wholly uncolored. 5 minutes after the dye injection the regions between these patches had for the most part changed from orange toward red, showing that the local acidosis was being dissipated; and the dye was slowly extending into the margins of the uncolored regions as a narrow zone of orange. After another half minute the remaining 8.4 cc. of blood was returned to the body. The pressure rose to 158 and soon to 168, near which high level it long remained. The coloration continued strikingly various. 7 minutes after the final injection of blood there were still many irregularly distributed, uncolored patches 1½ to 2½ cm. in diameter, of serpiginous outline. They were scattered thickly upon a background of varied hues, from carrot red to old rose, and at their periphery one could see a narrow zone, or edging, of ochreous buff. The marked increase in the blood pressure facilitated the passage of the stain into the tissues where circulation was taking place, with result that 11 min. after the last blood injection the patches were even more pronounced than before because of the deeper red of the background. The mucous membranes of the mouth were now eugenia red, and the pads of the paws pink,
evidence that there was no blood acidosis; but the hue of the stained superficial tissues had some orange in it here and there. After 14 minutes many of the spots were disappearing; and the general hue was light jasper red. After 18 minutes stain had entered all the remaining patches, coloring them an orange buff. The blood pressure had now fallen to its initial level, 140 mm. Hg. Some of the orange spots were still to be discerned 55 minutes after the last injection of blood; but they had gone after another 34 minutes, when the surface color was everywhere the same, a hue between eugenia red and old rose. The blood pressure meantime had varied between 140 and 166. The ether was purposely kept very light.

These observations in which phthalein was injected after the blood had again been returned make plain the fact that the obdurate ischecma cannot be due to an influence of the vital dye. It is no artefact. That the bloodless state existed prior to the injection of phthalein was clear, not alone from the failure of the latter to enter large areas here and there, but from the hue it took on at the edges of these areas, a hue indicative of preexisting local acidosis such as develops only when ischemia has endured some time (6). There were vague indications of a special patching of the pallid skin even before the return of the blood. The intensification of the patches after the final blood injection, which resulted from a deeper staining of the tissue between them, is no unique phenomenon. We have regularly observed it, and,—as one would expect,—even more pronouncedly, when the blood that was withdrawn and returned to the body contained dye.

Prior to a consideration of the causes for the persistent bloodless state the circumstances of its occurrence will be more nearly dealt with. Those leading to the initial patchy ischemia have been described in several previous papers (7). The patches develop in compensation for a reduced blood bulk, however brought about; and they appear only when the reduction has been considerable. The greater the depletion, the larger are the bloodless areas; and if it persists unrelieved they increase in size by peripheral extension. In animals gradually depleted by induced anhydremia they appear before any noteworthy reduction of the general blood pressure occurs; but in hemorrhage cases, they are best seen when the blood pressure has been substantially lowered. They occur in both urethanized and etherized animals but develop also in those bled under local anesthesia, a relatively great depletion being required to cause them in these last. They occur when the skin is kept warm artificially as well as when it has grown cold owing to deficient blood flow.
The persistence of the patching after return of the blood to the body is dependent, like its initial occurrence, on the degree of the depletion and its duration. The more the blood bulk is diminished, and the longer the elapsed period afterwards, the more obdurate does the patching prove.

**Experiment 3.**—A thin, white, female cat, with a few gray markings, previously depleted and fasted for 24 hours, was operated upon under ether to cannulate the trachea, right carotid artery and left jugular vein. The animal weighed 1950 gm. The operation took 15 minutes. The initial blood pressure was irregular varying from 120 mm. Hg to 150 mm. With the animal on its left side in an unconstrained position 56 cc. of blood was removed at three bleedings, by way of the cannulated carotid, in the course of 40½ minutes, reducing the blood pressure to 38 mm. at which low level it remained, until,—after 45 minutes in all,—7½ cc. of phenol red solution was injected, in 100 seconds. The animal appeared *in extremis* after 47½ minutes; and 2½ cc. of the heparinized blood was reinjected. Artificial respiration was necessary for a few breaths. It was given with the Gates' pump (8). Then the pressure rose to 50 mm. and natural breathing was resumed. After a further 2 minutes 3 cc. more of blood was injected, merely sufficient that is to say to maintain the animal. The vital staining was for some time nearly negligible except that the lips and gums, which had appeared bloodless, promptly became red after the injection of the phthalein; but little by little color crept in, and 12 minutes after the last blood injection (or 15 minutes after the phthalein) the surface was strikingly variegated with orange to red areas betwixt large unstained patches. The pressure had reached 60 mm. Hg. Now 3 cc. more of blood was given, and 7½ minutes later all the rest (in the course of 4½ minutes) except 9 cc. The pressure at once rose to 152 millimeters and the veins became notably distended, yet four minutes later the mottingling had not altered. Thereafter the red between the patches became accentuated and these slowly turned orange with dye entering them, and eventually they merged with the red of their surroundings. The last of them was not gone for about an hour. To the blood as it was withdrawn salt solution, containing 10 mg. of heparin (Hynson, Westcott and Dunning) in every cc. was added in the proportion of 1 cc. for 15 cc. of blood. What with this addition, the amount of fluid returned to the body, though 9 cc. less than the total of blood plus heparin, was only 5 cc. less than the total of blood removed. A large experience with the anticoagulant enables us to say that it does not of itself induce local ischemia.

In this experiment the animal was bled to the limit and the blood was only very gradually returned to the body after the injection of phenol red. At first the dye largely failed to enter the superficial tissue, and where it did so later the color indicated tissue acidosis. Needless to say the very low blood pressure will amply account for these find-
ings. Later on, when the unstained patches were smaller and well
demarcated, all of the blood except 5 cc. was gradually returned to
the body. Although the blood pressure mounted far higher than
before the bleedings, and there was a manifest plethora with engorge-
ment of the veins, the spotting persisted for an hour. These results
and those of Exp. 1 may be contrasted with the following:--

Experiment 4.—A well nourished, white female cat of 2540 gm. was prepared
and operated upon as in the case of Exp. 1, except that the removal of fur had been
done with the razor and the initial fast had lasted only 18 hrs. The cannulations,
der under ether, took 18 minutes. Thereafter the animal was bled 62 cc. in 54 minutes.
The blood pressure was reduced from 170 mm. Hg merely to 100 mm. Pallid
blotches on a generally pale skin became visible over the animal's right side—which
was uppermost; and 19½ minutes after the last bleeding 9½ cc. of phenol red was
injected (in 65 seconds). 4 minutes later the body surface was a brilliant pink
variegated with numerous, scattered white patches up to 2 cm. in diameter. The
return to the body of all the defibrinated blood was begun 11 minutes after the
dye injection and completed 3½ minutes later. The carotid pressure rose to 180,
at which level it remained, and there was the usual evidence of a plethora. Within
a minute the animal had stained much more deeply, and the spots stood out in
startling contrast; but they soon began to turn pink and within thirteen minutes
had disappeared. The cat was by now of a hue deeper than old rose.

In this instance although much blood had been taken the carotid
pressure remained fairly high and the blood was returned to the body
after only a short interval. The ischemic patches, while well defined,
had not endured long, for no acidosis had developed in them. They
stained pink, not orange, and quite rapidly.
To these contrasted findings may be added others of similar import
in rabbits. Very deep urethane anesthesia so impairs the circulation
that patching results, but ether does not do this unless pushed close
to the lethal limit (9). In the tests now to be described the animals
were bled with the aid of a local anesthetic, novocaine.

Experiment 5.—A white, female rabbit of 2400 gm. shaved over the trunk and
thighs 9 days previously was fasted 24 hours, and under ether the right common
carotid was brought to the surface and cannulated. The vessel was kept shut by
a special device made of rubber tubing (10), the pressure of which could be
relaxed at will and bleeding accomplished with the animal sitting naturally. The
incision was swabbed with novocaine and covered with a wet dressing. When
the animal was again up and about, after 63 minutes, novocaine was re-applied
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locally and the depletion begun. During the course of an hour and five minutes 76 cc. of blood was removed—at three bleedings—and at once defibrinated. Immediately afterwards the animal appeared in good condition, sitting in the normal posture; but it was found collapsed and apparently moribund 18 minutes later. The reinjection of all of the blood by way of an ear vein, and removal to a very warm room, benefitted it but little. Eight minutes later, at the time when 9 cc. of phenol red was given, it was still pallid and appeared unconscious, but after another eleven minutes it got to its feet. The superficial staining at this time was localized to localities where large vessels entered the skin (popliteal space, regions just back of the axilla and over the sacroiliac joint). Here the hue was orange. The animal was sitting up and in fair condition 51 minutes after return of the blood, yet the skin still showed completely unstained areas on a ruddy to orange ground. Along the ridge of the back was a well demarcated orange stripe. The general condition continued to improve, but 79 minutes after the blood injection the patches previously unstained were still to be discriminated, though now coral red on a jasper red background. At this time 7.2 cc. of warmed 4 per cent brom phenol blue was injected in 60 seconds. Most of the surface of the animal colored as rapidly as if the animal had been normal, becoming a deep plum color within three minutes, but very little of the dye had entered the patches at the end of this time. After a further 4 minutes, though, they were no longer to be discerned as such, having merged in the general hue.

The introduction of a second dye into this animal brought out the fact that there was still some persisting local ischemia 1½ hours after the blood had been returned to the body. During much of this period the general circulatory state had been poor. But the rapid distribution of the second dye everywhere in the superficial tissue except in the regions of ischemia clearly proved that these latter were not due to a faulty general condition.

In a second rabbit the phenol red was injected before the bleedings had all been wholly accomplished, with result that depletion was less drastic. The only patching obtained was one traceable to local pressure differences. Like the ischemia unlocalized by any such factor it persisted after return of the blood.

Experiment 6.—A male, white rabbit of 2175 gm. was employed which had been epilated over the trunk and thighs with barium sulphide some days previously. No inflammation of the skin had ensued. The animal was fasted for 24 hours, and then, under ether, the left common carotid was cannulated and obstructed with the same device as in Exp. 5. Prior to closing the incision the tissues were swabbed with novocaine. Fifty-four minutes after the operation had been completed the animal had recovered from the ether and was in excellent state. Now it was bled
28½ cc. in 75 seconds, and 30 minutes later another 21½ cc. in 110 seconds. There-
after the skin was pallid but still warm, and not blotched. After the lapse of
a further 32 minutes 12 cc. of blood was taken in 70 seconds. As each lot was
obtained it was defibrinated. Twelve minutes later 8.5 cc. of 4 per cent phenol red
was injected into an ear vein in 60 seconds. This caused no symptoms, and the
animal, which sat quiet, colored slowly and evenly. So well had the depletion and
staining been withstood that eighteen minutes later the rabbit was sniffing about
the laboratory floor as if nothing had happened. The general color was now old
rose save for large patches over the ridge of the backbone and the projection of
the knees where the hue was yellower. Since no patching developed in the next
twenty minutes a further bleeding of 15½ cc. in 3½ minutes was carried through.
Thereafter the patching over back, sides and haunches became more pronounced,
light coral red as compared with light jasper red elsewhere. The animal retained
the sitting posture but appeared listless. The entire quantity of blood, 77½ cc.,
was now reinjected in 185 seconds, thirty-three minutes after the final depletion.
The general condition immediately became excellent. Yet the patches persisted
unchanged during the next ten minutes, though the red about them became deeper,
approximating eugenia red. After another seven minutes those over the knees had
disappeared and the one along the backbone was fading at the edges. Twenty-
four minutes after the return of the blood the color was everywhere the same,
slightly deeper than old rose. Decolorization, which now began, proceeded swiftly
and so evenly as not to suggest that there had ever been patching. The rabbit
was alizarin pink one hour and forty-four minutes after the return of the blood and
still faintly pink three hours after. It was then discarded.

In this instance the removal under local anesthesia of about half
of the calculated blood volume did not suffice to bring about a general
patching, though the circulation was sufficiently cut down over back
and knees for some local acidosis to develop there, as the indicator
showed. The abnormal state of affairs was rendered more pronounced
by a further bleeding which the animal stood well. And now when all
the blood was reinjected and the general condition became excellent
the local acidotic patching failed to disappear for a considerable time.
That its obduracy was not due to factors effective under normal con-
ditions was shown by the course of the eventual decolorization which
took place at the same rate in the regions previously patched as it
did elsewhere.

It has been our frequent observation that local pressure conditions
of no moment ordinarily will lead in the depleted animal to a localized
ischemia indistinguishable, save in situation and in the extent and
shape of the patches, from that occurring elsewhere over the body (11).
Exp. 5 yielded an example of the sort, in the patching over the ridge of the backbone, while in Exp. 6 all of the patching was of such type. The ischemia tends to persist like that appearing elsewhere on the body and not evidently referable to any local pressure differences. We have enlarged the observations upon it because of the physiological problem presented by the persistent bloodlessness in general.

As has already been stated the etherized cats of the present investigation were placed on the back or side in postures naturally assumed and with the limbs free. Some regions were necessarily higher than others and in these regions,—over mid abdomen and chest, with the animal on its back, or over the upper side and flank, when it was on its side,—the spotting tended to last longest after return of the blood. When the cat was in the dorsal posture and the hind legs lay symmetrically half flexed with one knee slightly higher than the other, the ischemia persisted longer over this higher knee even though the difference in level was but two or three centimeters. The important influence of local pressure differences, as thus illustrated, was especially well to be seen when one of the legs had been raised for some time.

Experiment 7.—The cat was that of Exp. 3 (q. v.). It lay on the left side, but slightly toward the dorsum. In order to relieve the abdomen and chest from any pressure of the legs that were uppermost,—those of the right side,—a string had been looped around one toe-nail of each and tied to a support in such wise that the limbs were held suspended in the air in the same posture of partial flexion as their fellows. The suspended right foreleg must be dismissed from consideration since it had not been epilated. When the phenol red was injected, after the bleedings, as already described, no stain whatever entered the tissues of the raised hind leg for some little while, but by the time its fellow on the other side had become diffusely orange a well defined, horizontal color demarcation had developed in it just distal to the groin, approximately 5 cm. above the well stained thigh. Above this level the tissues of the leg were pallid and unstained, below it orange. The zone of transition was about 0.6 cm. broad. The femoral vein of the raised leg was noted to be collapsed, that of its fellow distended. Eleven minutes after the return of the blood, when the general body surface was a brilliant pink with scattered orange spots, there was still not the least staining of the suspended leg. The blood pressure had been far above its initial height since the re-injection of the blood. After a further six minutes the line of demarcation had disappeared and phthalein was extending upwards into the skin of the leg, staining it orange (or apricot buff in Ridgway’s nomenclature). The animal was by now old
rose with scattered apricot buff patches. Thirty-eight minutes after return of the blood the highest part of the raised leg, the region around the knee, was still only faintly stained (pale buff). This region was 10 cm. above the midline, as the animal lay, but only 3–4 cm. above the highest part of the side. In this part the color had a slight admixture of yellow as compared with the diffuse old rose seen elsewhere. The wide-spread spotting had disappeared. The blood pressure had fallen somewhat (from 152 mm. to 134 mm.) but was still above the initial level (120 mm.). The animal had now been under ether for more than two hours.

Experiment 8.—The cat of Exp. 1 (q. v.) served for the observations. It lay on the back under light anesthesia with the legs symmetrically rotated outwards and half flexed. They never became flaccid and hence did not touch the table at all. The right knee was slightly higher than the left. After the injection of the phenol red the tissue for a wide space about the knee was observed not to stain at all, and it remained unstained when the blood had been returned to the body, although the carotid pressure was raised thereby to a much higher level than it had been originally (160 mm. as compared with 142 mm.) and there occurred a wide-spread staining elsewhere. Ten minutes after the injection the superficial tissue about the knees was still uncolored and one could perceive after oiling the skin that this held true of the underlying muscle as well. Yet the main artery of the limb was beating far more violently than usual, owing to the induced plethora, and the pads were red. After another fifteen minutes traces of dye were entering the ischemic tissue, rendering it buff at some places. Elsewhere in the leg one could perceive through the oiled, unstained skin that the large subcutaneous veins were darkly red, with a pink diffusion of dye immediately next them. The animal was in general ruddy, but spotted irregularly with pale orange buff. The blood pressure had remained high. Both legs had attained the same ruddy hue after 44 minutes in all. There was still much spotting over the chest and abdomen. 40 cc. of warmed Ringer's solution was now injected to increase the plethora, and thereafter the spotting soon disappeared.

In these instances the slight circulatory difficulty produced by raising the leg a few centimeters above its fellow sufficed, not merely to render it ischemic after the depletion but to ensure the persistence of the ischemia later, when the blood bulk had been restored and the blood pressure had been brought so high that the circulatory difficulty just mentioned should have been wholly negligible. In Exp. 8 there was an obvious plethora after return of the blood; the main artery of the ischemic limb beat violently, the paw was well stained, and the venous blood deeply so. Yet the tissue previously ischemic remained for some time obdurately bloodless.

Needless to say the factor of local chilling had to be considered as possibly favoring a persistence of the bloodless state, however caused.
The ischemic tissue became cold. So too, if in a less degree, did the body surface patched with ischemia. But that the development of such patching is not essentially dependent upon cooling has been sufficiently shown by immersing animals in oil at body temperature (12). The cats in which its persistence was studied were often long on the table, and care had to be taken to keep them warm in order to prevent shock.

The question whether the spots recur at the same places after a second bleeding is one of great importance for an understanding of them. Many experiments were done upon this theme, a principal difficulty being the long interval required for complete disappearance of the local ischemia after the blood of a first depletion had been returned to the body. It was necessary to recognize and rule from consideration the patching due to local pressure differences (of the sort illustrated by Exps. 7 and 8); for such patching infallibly recurred unless the position of the animal had been changed. Needless to say this recognition and ruling out could not always be perfectly done. Furthermore there were spurious patchings to be discriminated, as where underlying fatty masses made the skin appear pale, or where the circulation was naturally poor, as about the umbilicus. In regions of local inflammation the staining was always far better than elsewhere; but such regions were always readily discriminated. Abrasions with the razor give rise to a staining that is on the actual surface, not beneath it as in the case of the cutaneous staining proper.

The general plan was to use phenol red to disclose the patchings of a first depletion, which were then marked out here and there with dots of india ink; and after restoration of the blood and a second bleeding, —sometimes indeed after return of the blood for the second time,—brom phenol blue was injected. This dye diffuses swiftly and is more easily seen in the tissues than is phenol red; and hence the pallid patches demonstrated with its aid often appear smaller than when the latter dye has been used—the more especially since this turns orange in acidotic tissues. The animals were usually bled to death from the carotids while the ischemic patching of the second depletion was still evident; and the pelt was at once stripped to determine the relation of local features to the patching.
Experiment 9.—The cat of Exp. 1 (and Exp. 8) was kept warm and under light ether until all the patching of the first depletion had disappeared. As the protocol of Exp. 8 shows, the process seemed to be hastened by the increase in plethora brought about through the rapid intravenous injection of 40 cc. of warmed Ringer's solution 54½ minutes after the last blood injection. However this may be, a second series of bleeding was begun 141 minutes after the start of the first. The outlines of fourteen of the characteristic patches induced by the first depletion had been marked on the skin with small dots of india ink. The body surface was diffusely stained old rose at the time when the new bleedings were begun. The carotid pressure was 144 mg. Hg, the initial pressure having been 142. Hemorrhages of 43 cc. in 19 minutes now caused it to fall to 78 mm. Within 15 minutes after the initial hemorrhage (of 33 cc. in 4 minutes) the phthalein in the tissues turned toward orange where some of the marked spots had been; and 3 minutes after the second bleeding (of 10 cc. in 1½ minutes) the spots had become accentuated and numerous others were present in unmarked regions. The general color was between light jasper red and alizarin pink. The body surface was warm. The pressure rapidly recovered to 90 but fell to 82 when a further 3 cc. of blood was taken, 5½ minutes after the second bleeding; and it had not risen 2 minutes later when 6.6 cc. of brom phenol blue was injected in 50 seconds. This raised the pressure to 94 but it had again fallen to 78 when, after 8 minutes more, the entire quantity of defibrinated blood, less 2 cc., was reinjected in the course of 95 seconds. The pressure rose from 76 to 140 mm. in the course of 4 minutes. The general condition of the animal was excellent.

During the interval after the injection of the brom phenol blue and prior to return of the blood a patchy staining of the superficial tissues occurred, superimposed upon that with phenol red. There were numerous scattered splotches into which the new stain did not enter, and the plum color of the regions between was not diffuse but dappled with small spots of dirty yellow which the brom phenol blue had failed to penetrate. Following return of the blood these ischemic yellow splotches stood out pronouncedly, owing to an increased staining of the tissue between them. A count made 3½ minutes after the injection of the second stain showed that 8 of the 14 areas previously marked with ink dots were present as such splotches, but of these 8 two were near the projection of the ensiform cartilage and might have owed their freedom from the blue phthalein to local pressure differences. Five marked areas had stained somewhat, and one was not to be discriminated from its surroundings, being deeply colored. The spots that recurred were not accurately reproduced in the original form, and were in general somewhat smaller. The body surface elsewhere was abundantly spotted. Yet the recurrences within inked outlines were too definitely related to these latter to have been due to chance.

Twenty minutes after the blue phthalein had been given the animal was killed by cutting the carotids. The blood pressure at the time was 128 mm., and the ischemic spots had persisted. At autopsy no local factors to account for them could be found. Numerous others were visible in the furred skin when this was stripped back.
These findings, representative of several experiments, leave no doubt that some of the ischemic patches recur in the same situations after the second depletion, though this is far from being true of all. The injection of brom phenol blue had not been necessary to demonstrate the fact in the instance just given in detail. For the animal was still stained with phenol red after the blood was withdrawn for the second time; and patchy changes toward orange, the color indicative of local acidosis, evidenced a recurrence of the local ischemia in the previous situations.

The circulatory readjustment following the first return of blood was in some cases completed only after the animal had been under ether for several hours altogether. In these cases a singular pattern ing with brom phenol blue resulted, one wholly different from any observed after depletion under ordinary circumstances, no matter how severe this had been or to how low a level the blood pressure had been reduced.

Experiment 10.—The cat of Exp. 2 still showed some spotting 55 minutes after the first reinjection of blood, and 126 minutes after the initial bleeding. Only after another 38 minutes had the staining become diffuse, the color being then slightly darker than old rose. The blood pressure was 166 as compared with 140–145 at the beginning. Now, 206 minutes after the initial etherization, 61 cc. of blood was taken, at three bleedings in the course of 57 minutes, reducing the blood pressure to 72. Twelve minutes later the surface was mottled with buff spots on an irregular ground of coral pink and old rose. 6.6 cc. of 4 per cent brom phenol blue was injected in 75 seconds, and 5 minutes later all the blood was returned to the body, in the course of 180 seconds. The animal began to stain promptly, a plum blue reticulum enclosing greenish yellow patches averaging about 1 cm. in diameter. A count made 9 minutes after the dye had been given showed that only 6 out of 13 areas ischemic previously, and marked as such with india ink, were unstained by the blue phthalein, the other 7 being as deeply, if irregularly, colored as the tissue anywhere else. One could not be certain that the sparing of even these 6 was due to anything but chance, since ischemic patches were everywhere very numerous. Later the 6 largely lost shape through an irregular encroachment of the plum color. Twenty-eight minutes after the injection of the blue phthalein, and 262 minutes from the time of the initial bleeding the blood pressure was as high as at first (140 mm.). The superficial staining had now assumed a regular pattern, thick purple meshes separating rounded areas of dirty greenish yellow about 1 cm. in diameter. This fish-net mottling persisted practically unchanged throughout the next 40 minutes during which the carotid pressure declined to 130. In the course of the next hundred minutes the mottling largely disappeared, but
not wholly. The experimentation had lasted more than 7 hours. At its end the
blood pressure was only 95, the rectal temperature 98.6
The disappearance of the reticulum took place by an entry of the blue dye here
and there into the greenish yellow spots, breaking them up into irregular areas 3-4
mm. across. Thus the body surface became thickly strewn with little ischemic
patches. These very gradually acquired stain and disappeared.

This experiment, one of several with similar results, yielded evidence
of a change in the character of the blood service to the superficial
tissue of animals long on the table. But its principal use in the present
connection is to illustrate a difficulty met in determining whether
local ischemia tends to recur in the same situations.

DISCUSSION

The original aim of the work here reported was to learn whether
the ischemic spotting which develops after depletion affects the same
regions when depletion is induced once again. Our evidence for the
obduracy of the ischemia is the more convincing because unexpected.
In the literature one finds few signs to suggest that such a phe-
nomenon exists. The methods have not been fitted to disclose it.
Yet bedside practice from immemorial times has allowed for it as a
possibility. The old wife customs of chafing bloodless extremities,
and applying heat to them, are still in current use to “restore the
circulation,” on the assumption that restoration might long be delayed
without such help.

Zak (13) has described a blanching of the fingers when they are
exercised after the circulation to them has been cut off. He believed
this due to an active contraction of the small vessels, but Rehberg and
Carrier (14) hold that the blood is merely forced from the fingers me-
chanically. These authors do not deal with Zak’s further observation
that the vessels contract in a frog muscle exercised while the circula-
tion is stopped, failing for some time to admit blood again when the
impediment is removed. Whatever the explanation of this latter
phenomenon the circumstances of its occurrence are essentially differ-
ent from those of the one we have studied. Not so however with the
patchy areas of ischemia of the human skin known by the name of
Bier’s spots (15). These areas of local contraction of the small vessels
develop gradually when the circulation to a congested limb is cut off
by means of a pressure cuff; and they are evident as blanchings in the midst of a venous hyperemia. In our animals the local cessation of blood flow was induced by depletion, not by a cuff, and the regions of ischemia were demonstrated with a diffusible stain. The numerous reasons for identifying the ischemic patches of our animals with Bier's spots will be detailed in a subsequent paper. Lewis (16) states that the best-developed spots tend to resist the sudden influx of arterial blood after release of the cuff, which floods the arm with the bright pink of active hyperemia. In our own experience with many subjects and numerous trials this resistance has never lasted long. Most of the blanched spots disappeared at once in the flush, and those which did not faded rapidly from the periphery in the course of a minute or two. But it has seemed unwise to cut off the circulation from the arm for more than 45 minutes. The short period of occlusion when taken in connection with the relatively slow metabolic activities in man as compared with the cat, may explain the differing persistences of the ischemia.

Bier (17) pointed out that the pallor of the dead body is due to a generalized contraction of the small vessels, similar to that manifested locally on the living subject in the blanched spots now called after him; and Lewis holds that the dead whiteness of the fingers in Reynaud's disease is referable to the same cause. Our observations bear out these assumptions, and give ground for a further one, namely that much of the difficulty in restoring the circulation to parts temporarily deprived of blood, as in Reynaud's disease, chilblains and skin threatened with bed-sores, comes from a vascular perversion secondary to the initial ischemia. Whether this perversion occurs in those instances of shock and hemorrhage which continue to show a pallid, cold skin despite transfusion and other active measures remains to be seen. The cause for the phenomenon here reported will be discussed in a later publication. It is scarcely necessary to remark that the length of time during which the ischemia lasted in our experiments did not nearly approach that required to cause frank injury of the tissues. Furthermore the deprivation was the result, not of arbitrary interference with the circulation, but of compensatory readjustments within the organism such as would tend to prolong life.
SUMMARY

In skin regions which have been bloodless for some time, as result of the functional readjustments following upon a reduction of the blood bulk, the ischemia persists long after the blood volume has been restored and the systemic blood pressure has mounted to the initial level or a higher one.

The significance of the finding is briefly discussed.

BIBLIOGRAPHY