Summary

A study has been made of the nasal organ of fish, with particular reference to the distribution of olfactory mucosa and of secretory epithelium. A comparison is made with the nose of mammals, in which there is typically an anterior air-conditioning part and a posterior olfactory region.

Observation of a representative series of mammals reveals a correspondence between the olfactory and the humidifying areas and indicates a relation between the two, both areas being small in species with feeble powers of scent and extensive in keen-scented animals.

The epithelium generally known as respiratory is found to be of two types, one ciliary and the other thin and permeable.

The conclusion is that the present views on nasal physiology require readjustment.

Figs. 1, 2, 3, and 5, and the Table, appeared in *Annals of Royal College of Surgeons of England*, 1954, vol. 15, Sept., and Fig. 4 in *Acta Oto-laryngologica*, 1955, vol. 44, Fasc. 5-6.

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ACUTE PERIPHERAL CIRCULATORY FAILURE IN SURGICAL CASES TREATMENT WITH L-NORADRENALINE

BY

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The term "peripheral circulatory failure" is often used to describe a clinical state in which there appears to be widespread stasis of blood in the small cutaneous vessels, with a noticeable reduction in the speed of reflux into the capillaries after finger-tip pressure. It is associated with a patchy cyanosis, particularly marked at the extremities, with a rapid thready pulse, and with hypotension. This type of response may be observed clinically in many different conditions. Among these are coronary thrombosis, fulminating infections, extensive burns, intestinal strangulations, grave electrolyte upsets, peritonitis, acute pancreatitis, and after aspiration of vomitus. It has been thought that various agents such as vasodepressors and bacterial toxins may be responsible for the phenomenon, but convincing proof is lacking. For a complete understanding of this condition, further work remains to be done on the response of the peripheral vessels, and on blood-volume shifts.

Clinical observation suggests that dilatation and stasis occur in the vessels of the skin. It seems likely, also, that blood is sequestered in the subcutaneous tissues, which are seen to contain sluggishly moving, poorly oxygenated blood if operation is undertaken during this phase. The appearance of the seromuscular coat of the bowel suggests that therein also the vascular bed has dilated and stagnation is occurring. If these observations are correct one might anticipate improvement after administration of a peripheral vasoconstrictor.

Studies of the pharmacological properties of L-noradrenaline have suggested that it may be capable of increasing peripheral vascular tone. It has been shown that this drug is an overall vasoconstrictor in man, producing secondary increases in both systolic and diastolic pressures, but without directly increasing cardiac output, and having none of the untoward central effects of adrenaline itself (Goldenberg *et al.*, 1948; Swan, 1949; Churchill-Davidson, 1951a). Vasoconstriction has been observed in the vessels of the seromuscular coat of the colon in man after L-noradrenaline (Grayson and Swan, 1950). Swan (1952), after a study of blood flow through various organs, concludes that it would be the drug of choice in peripheral circulatory collapse.

The Investigation

An attempt was therefore made to assess the effect of L-noradrenaline on acute peripheral circulatory failure occurring in surgical cases. I have used the drug in 14 such cases of varying aetiology. In all but one of these a response was obtained. All had systolic blood-pressure levels of 60 mm. Hg or below, and levels of 90-100 mm. Hg were attained within one to five minutes. These levels were maintained for periods of up to 48 hours. It is, however, difficult to control such an investigation. Peripheral circulatory failure is not a disease entity in itself, but is a vascular phenomenon which may arise during the course of many different illnesses. It is not, therefore, possible to treat it as a single pathological condition, and so to estimate the efficacy or otherwise of treatment. The underlying causal process must always modify and cloud the evaluation.

This difficulty can to some extent be overcome by confining the study to cases of one specific type, preferably where treatment of the primary lesion is possible only if the failure can be relieved. For that reason a group of four of these cases are considered in some detail where failure had come on rapidly after gross faecal or purulent contamination of the peritoneal cavity. This gives the added advantage that the degree of circulatory collapse was profound and surgical correction could be attempted only if this was overcome. This group includes that case in which no response was forthcoming.

We have regarded acute peripheral circulatory failure as being present in this group when, within a few hours, the skin had become cold, blue, and blotchy, when the speed of reflux into the cutaneous vessels after digital pressure was greatly reduced, when the pulse was faint and rapid or imperceptible, and when the systolic blood pressure was below 50 mm. Hg or not recordable. From the fact that this state developed rapidly after a proved abdominal catastrophe and that clinical and E.C.G. confirmation was lacking both then and later, we have assumed that coronary thrombosis was excluded.

Case 1

A man aged 52 was admitted to hospital at 8 a.m. on January 4, 1954, complaining of hypogastric pain which had come on suddenly 10 hours before. He gave a history of intermittent constipation and loss of appetite for one month. Clinically he showed signs of diffuse peritonitis. His pulse was weak and rapid, B.P. 50/30 mm. Hg, and marked signs of peripheral circulatory failure were present. At 8.30 a.m. an L-noradrenaline drip was started at 4 µg./min. This was increased to 8 µg./min. as the response was poor, and by 9 a.m. his B.P. had risen to 90/50 mm. Hg.

Laparotomy was carried out and the peritoneal cavity was found to be full of faecal material. This had come from a perforation of a carcinoma in the distal part of the pelvic colon. Exteriorization was not possible, as the patient's condition was giving rise to concern. The proximal part of the pelvic colon was brought out as a defunctioning colostomy and a drain was inserted into the pelvis. During operation the response to the drug lessened and the dosage

was increased to 12 $\mu\text{g./min.}$ His condition never improved post-operatively in spite of larger doses of the drug, and his B.P. fell to 40/? mm. Hg at 9 p.m. One hour later he died. Post-mortem examination had nothing to add to the operative findings.

Case 2

A man aged 78 was admitted to hospital on January 16, 1954, with a history of having had a hernia manually reduced by his medical attendant 24 hours previously. The hernia was of the right inguinal variety and apparently had come down into his scrotum some days before this. He had taken two doses of a purgative since this was done, but his bowels had not moved. On the morning of admission he had begun to hiccup and had vomited once. Shortly before he came to hospital he had become semicomatose. On examination he was found to be comatose and pronounced signs of peripheral circulatory failure were present. His pulse was imperceptible and his blood pressure could not be recorded. His abdomen showed diffuse tenderness and tympanites. Bowel sounds were absent. Intravenous infusion of noradrenaline was given, 4, 8, 12, and 20 $\mu\text{g./min.}$, without effect on his hypotension. Five hours later, in spite of continuous infusion of noradrenaline, the patient died.

At post-mortem examination a loop of ileum was found to be gangrenous and perforation had occurred. There was gross peritonitis, and the peritoneal cavity contained much faeculent fluid.

Case 3

A woman aged 68 was admitted to hospital on March 3, 1954, with a history of malaise and shivering attacks for 12 days and vague upper abdominal pain for six days. On examination a large rounded intra-abdominal swelling was found below the left costal margin. The swelling was smooth and soft, and moved on respiration. It was tender to the touch but did not seem to be definitely fluctuant. X-ray, biochemical, haematological, and blood-culture investigations did not prove helpful in reaching a diagnosis. On the morning of March 6, however, she felt less well, and at 2 p.m. she complained of sudden widespread abdominal pain and her general condition showed marked deterioration. Within 30 minutes she had developed signs of peripheral circulatory failure and her blood pressure had fallen from 160/70 to 90/30 mm. Hg. Fifteen minutes later she became semicomatose and her blood pressure was found to be 50/?. A noradrenaline drip was started at 4 $\mu\text{g./ml./min.}$ Within 30 seconds her pressure rose to 130/60 mm. Hg and it was decided to carry out a laparotomy.

At operation the peritoneal cavity was found to be filled with foul-smelling greenish-yellow pus, which had come from an abscess in the upper surface of the left lobe of the liver, having a cavity large enough to admit a closed fist. Toilet of the peritoneal cavity was completed and the abdomen was closed with drainage of the abscess and of the pelvis. During operation the B.P. was controlled at 110/60 mm. Hg by an L-noradrenaline drip. Within 48 hours she was able to maintain her blood pressure at satisfactory levels without the drug. Bacteriological examination of the pus showed the presence of an anaerobic streptococcus, sensitive to the broad-spectrum antibiotics but resistant to penicillin. Intravenous oxytetracycline, 1 g. daily for five days, was given. The patient made a satisfactory recovery.

Case 4

A man aged 33 was admitted to hospital at 11 p.m. on October 27, 1954, with a history of intermittent intestinal colic and increasing constipation for four months, loss of appetite for three weeks, and slight loss of weight. A barium enema two weeks previously had shown nothing abnormal. On examination abdominal distension, tympanic in nature, was noted, mainly in the flanks. Increased bowel sounds were heard, and rectal examination was negative. Straight x-ray examination of the abdomen in the erect position showed multiple fluid levels in both small and large bowel. At laparotomy a carcinoma was found to be obstructing the first part of the pelvic colon. There was no evidence of dis-

semination. A caecostomy was performed. This decompressed the colon satisfactorily. Ten days later he began to have occasional attacks of colicky hypogastric pain, and on November 9 he passed a little faeces per rectum. The colicky spasms remained troublesome, though he showed no distension and his caecostomy functioned normally. In view of this upset, resection was temporarily postponed and an expectant course taken. By November 18 his symptoms had subsided and a decision was taken to carry out the resection in a few days' time.

At about 10 p.m. on November 20 he complained of abdominal pain and vomited bilious material. Examination of the abdomen revealed no abnormality and bowel sounds were present. At 8 a.m. on the 21st his condition deteriorated suddenly with further vomiting and left-sided abdominal pain. Within an hour signs of peripheral circulatory failure appeared and the B.P. fell to 100/50 mm. Hg. There was some tenderness in the left flank but no marked physical signs in the abdomen. In view of the presence of bowel sounds and the absence of signs of peritoneal irritation, and since his caecostomy had discharged freely throughout, it was thought wise to try to exclude cardiac or pulmonary causes. X-ray examination of the chest and electrocardiography showed no abnormality. At 1 p.m. his B.P. had fallen to 30/0 mm. Hg and the signs of cerebral anoxia were observed.

An L-noradrenaline drip was started at 4 $\mu\text{g./ml./min.}$ Within 60 seconds a response was noted, the B.P. rising to 70/? mm. Hg. After five minutes it was controlled at 90/30 mm. Hg. One hour later, at laparotomy, a small abscess was discovered in relation to two diastatic perforations of the lower end of the descending colon. The abscess had ruptured into the peritoneal cavity and faecal contamination had followed. Toilet of the abdomen was carried out. A de Pezzer catheter was stitched into the bowel at the site of the perforations and the area extra-peritonealized. The infusion was continued during the operation, the blood pressure being maintained at 100/40 mm. Hg for 48 hours post-operatively, by which time his circulation had re-established itself. Intravenous oxytetracycline, 1 g. daily for five days, was given. Resection with end-to-end anastomosis has since been carried out and his caecostomy has been closed.

Discussion

Dosage

No cut-and-dried dosage can be laid down. The correct dose is that which raises the pressure to the desired levels and maintains it there. This will vary from case to case and also during treatment.

In preparing such patients for surgery it has been our practice to content ourselves with systolic pressures in the region of 90–100 mm. Hg and to forgo increasing the dose in attempts to reach physiological pressures, unless these are quickly attainable. In the majority of cases of severe peripheral failure this level (90–100 mm. Hg) is obtained rapidly and easily, usually within the first hour. To secure a further rise to the normal range, up to 100% increase in the amount of pressor drug may be required, and three hours or more may pass in this manœuvre. It will prove impossible in some patients. We have preferred to proceed to surgery as soon as anaesthesia could be induced without undue risk. Shanahan (1955), however, believes that sufficient should be given to restore the B.P. "to the patient's usual level, if previously known, or 130 mm. Hg if not." During the period of recovery the amount given may be gradually reduced if the B.P. is not thereby affected.

Technique of Administration

West (1952) studied the stability of the drug. He recommended that, since it is rapidly oxidized in an alkaline medium, it should be given in 5% dextrose or saline containing ascorbic acid. Significant losses in activity occurred when saline alone or whole blood was the vehicle for infusion. After six hours, whole-blood dilutions were only 88% and saline only 83% effective. Preparations of oxytetracycline and tetracycline available for intravenous use are

heavily buffered with propylene glycol. A Y-piece, or preferably another vein, should therefore be used when these are to be given at the same time.

Two mg. of "levophed," which contains an antioxidant, is put up in 500 ml. of 5% dextrose (strength 4 μ g./ml.) and attached to a polythene tube well advanced into an ankle vein and tied there. This gives less risk of extravasation or stoppage. The B.P. is taken and the drip begun cautiously at 20 drops a minute (4 μ g.). As soon as the pulse becomes palpable or shows an increase in amplitude the B.P. is read again, and at all events after two minutes if no change is noted. The speed of the drip is then adjusted to meet the B.P. requirements. Obviously, care must be taken with this type of infusion, and B.P. and pulse rate recorded at five-minute intervals for the first hour. Both patient and drip are then placed under constant surveillance and B.P. readings taken hourly, or more often if possible, thereafter.

For prolonged administration the daily metabolic fluid and electrolyte requirements must be borne in mind. In our cases we have given a total of 3 litres per day or more if the stomach aspirate was appreciable—half as 5% dextrose and half as normal saline. To do this it is simpler to use two intravenous infusions; this has the disadvantage of adding to the patient's discomfort, but it is a much more satisfactory method, for the following reasons. (1) The dose of noradrenaline which may be given is dictated by the level of the patient's B.P. and not by his fluid and electrolyte requirements. Further amounts of parenteral fluids may be necessary, and these can most simply be administered by a second route. (2) It allows to be given saline and other solutions that might interfere with the potency of the pressor drug if it had to be given along with them. (3) If, as is often required in these cases, an intravenous antibiotic is to be used, it provides a simple means of doing so without inactivating the noradrenaline. (4) It provides a second available route if the vital drip carrying the active drug should fail.

If concentrations of 8 μ g./min., or above, are being used it is better to double the amount of drug put up in each 500-ml. bottle. Careful note should be taken of any ensuing alteration in the volume given as the active fraction, and compensatory adjustments made in what is given by the alternative route.

Signs of Recovery

These may be observed if the failure is still "reversible." Within the first few minutes a rapid and sustained rise in pulse volume and B.P. will be noticed, with a lessening in the pulse rate and in the manifestations of cerebral anoxia. This will be followed in the first hour or so by an increase in the speed of the cutaneous capillary reflux after finger-tip pressure. A warm moist red flush then appears in skin previously noticed to be cold, blue, and blotchy. Within 12 hours the urinary output will rise noticeably. Later the rate of the drip may be reduced without ill effect and "trial stopping" of the infusion attempted. A lengthening of the time before fall in the B.P. occurs suggests increasing activity in peripheral tone and is the harbinger of recovery.

Overdosage and Toxic Effects

Overdosage does not appear clinically to constitute as great a hazard as might be feared. Levels of up to 20 μ g./min. have given no ill effects (Swan, 1949).

Bradycardia.—Bradycardia, reflex in nature, occurs with exaggerated and unphysiological B.P. levels (Goldenberg *et al.*, 1948; Swan, 1949; Barcroft and Konzett, 1949; Barnett *et al.*, 1950). It is abolished by atropine. It was observed in two cases, not in the above group, with doses of the order of 20 μ g./min. Both patients were suffering from acute peripheral circulatory failure. A reduction in the amount given relieved the slowing.

Idiosyncrasy.—A case is recorded with marked hypertension round about 230/150 mm. Hg from a dose of 8 μ g./min. for 4½ minutes (Allison *et al.*, 1949). This was accompanied by bradycardia, stabbing retrosternal pain, violent pulsating occipital headaches, pallor, and profuse

sweating, but with no clouding of consciousness. These resolved after withdrawal and left no untoward effects.

Acute Dilatation of Stomach.—This complication is reported with 24 μ g./min. in a case of pulmonary embolism under treatment, but disappeared when the dose was reduced to 16–20 μ g./min. (Wolff, 1954). The diagnosis here must be open to some doubt on the evidence presented, but it was noticed that vomiting and distension occurred when the dose was increased for the second time.

Local Tissue Necrosis.—Extravasations at the site of infusions may produce local tissue necrosis, due to intense vasoconstriction (Greenwald *et al.*, 1952; Kurland and Malach, 1952; Bergmann, 1953; Miller *et al.*, 1953; Hall, 1955). It therefore seems wise to employ polythene tubing in these infusions. The presence of diabetes mellitus or obliterative vascular disease calls for further caution (Kurland and Malach, 1952).

Ventricular Fibrillation.—It is recommended that the drug should not be used in conjunction with cyclopropane or any anaesthetic which increases cardiac irritability, because of the risk of ventricular fibrillation (Papper and Cahill, 1952; Johnstone, 1953). It has been shown that both adrenaline and L-noradrenaline first increase and then depress the vulnerability of the canine ventricle to fibrillation (Hoffman *et al.*, 1955).

Renal Damage.—It is thought that noradrenaline should be avoided in cases of renal damage as it may produce renal vasoconstriction (Barclay *et al.*, 1947; Barnett *et al.*, 1950; Churchill-Davidson, 1951b). This is of secondary importance when it is being used as a life-saving measure. Recovery, ascribed to L-noradrenaline, was obtained in 17 cases of shock due to varying causes, in all of which anuria was present at the outset. None of these showed residual evidence of significantly impaired renal function (Skelton *et al.*, 1952).

Hepatic Ischaemia.—From experimental studies on liver blood flow, Grayson and Johnson (1952) believe that infusions of longer than an hour or two may be dangerous, on the grounds that noradrenaline produces liver ischaemia. Their findings were at some variance with those obtained in perfusion experiments on the canine liver (Andrews *et al.*, 1955). Bearn *et al.* (1951) found no decrease in flow during administration. At all events, the drug has by now been used clinically for periods up to 22 days with no untoward effects, a total of 1,452 mg. having been given (Hall, 1955). (See also Wise *et al.*, 1952; Kurland and Malach, 1952; Gazes *et al.*, 1953; Livesay and Chapman, 1953; Moyer *et al.*, 1953; Sampson and Zipser, 1954; Sokoloff *et al.*, 1954.)

Even if it can be shown that L-noradrenaline produces a direct reduction in renal and hepatic blood flow in the normal animal, when failure is present the haemodynamic responses are more complex. It may be that the rise in peripheral resistance returns to the general circulation large amounts of blood stagnating in the peripheral vessels, so that the effective circulating blood volume is supplemented and the venous return increased. Moreover, it is recognized clinically that there is a marked rise in the volume of urine secreted (Skelton *et al.*, 1952). This has also been our experience in the hypotensive states, and is objective evidence of augmented renal blood flow. It would be a bizarre physiological response if the liver did not benefit likewise.

It appeared that auricular fibrillation occurred during treatment of a man aged 70. This man had no previous history of heart trouble, and no clinical evidence of a cardiac lesion had been evident on admission. He was suffering from peritonitis of 48 hours' duration due to perforation of a peptic ulcer and had been treated for a further period of 48 hours with doses of 4–8 μ g./min. This maintained his B.P. at 110/70 mm. Hg. His pulse rate then became irregular, and an apex-wrist deficit of 37 per minute (120–83) was counted. The infusion was stopped and the B.P. fell to 80/60 mm. Hg. Five minutes later normal rhythm had returned. E.C.G. tracings were not obtained. It may be that these were in fact ventricular extrasystoles.

but the clinical impression, particularly in view of the apex rate, was that of auricular fibrillation, which does not seem to have hitherto been reported.

Clinical Results

A common feature in these four cases was the severity of the peripheral circulatory failure. In Cases 1, 3, and 4 anaesthesia and surgery would have been impossible without strenuous supportive measures. It cannot be assumed that intravenous therapy would have failed to make operative intervention possible. It has not been our experience, however, that a rise in B.P. comparable to that obtained in Cases 3 and 4 will be seen in anything like so short a time with inert infusions. Moreover, there is the risk of pulmonary oedema in cases of this type, where large amounts of fluid have to be given in attempts to raise the B.P. to satisfactory levels. No more than a few millilitres of intravenous fluid containing active principle was given in Cases 3 and 4 before the B.P. had reached levels compatible with anaesthesia. It is assumed that this rise was not due to the volume of these infusions. In both these cases more fluid was, of course, given in the post-operative period, when a degree of paralytic ileus supervened, and

Chart showing effect of temporarily stopping the infusion. Case 3 at 24 hours after operation.

gastric suction had to be employed. It was, however, noted in Cases 3 and 4 that 24 hours after laparotomy, toilet, and drainage of the peritoneal cavity, and after continued intravenous infusions and antibiotic cover, neither patient's circulation was sufficiently re-established to maintain adequate blood-pressure levels when the noradrenaline infusion was stopped. Withholding the drug at this stage produced circulatory collapse within 60 seconds, as measured by a rapid fall in systolic blood pressure, deterioration in the general condition, and recurrence of the signs of cerebral anoxia. Recommencement of the infusion rapidly corrected these changes (see Chart). These observations suggest that the pressor agent was effectively maintaining the blood pressure.

Where the extravasation had been present for longer periods the response to L-noradrenaline was less dramatic (Cases 1 and 2), and in general the degree of the response to L-noradrenaline was in inverse proportion to the duration of the peritoneal contamination. There was no response when soiling had been present for 24 hours (Case 2). It seems that a stage is reached in these cases where L-noradrenaline loses its effect, and, so far as this drug is concerned, the condition had become "irreversible." This probably occurs at about 12 hours after such pollution of the peritoneal cavity (Cases 1 and 2).

The rapidity and degree of response to L-noradrenaline appear to be of some prognostic significance. Where a good rise in B.P. to levels compatible with anaesthesia was obtained within one to two minutes of starting the infusion the outlook was good (Cases 3 and 4). Where the response was slower but still significant the ultimate result was disappointing (Case 1). Where there was no response the prognosis was, of course, unaltered (Case 2).

I have never found it necessary to give more than 1,500 ml. a day as the vehicle for infusing the drug. At any time this can be reduced by increasing the concentration of the drug in solution, if it is feared that too much fluid may be given. Overloading of the pulmonary circulation has not been observed in these 14 cases. Indeed, more fluid and electrolytes have usually had to be given to maintain normal balance.

There should be no question of pulmonary oedema arising with this regime. Should it occur it is clearly due to overtransfusion and not to the drug itself, which can, if necessary, be given in a negligible volume of fluid.

Summary

An attempt was made to assess the effect of L-noradrenaline on acute peripheral circulatory failure occurring in surgical patients.

From a series of 14 cases, in 13 of which a response had been obtained, a homogeneous group of four is presented in some detail, in which failure followed gross faecal or purulent contamination of the peritoneal cavity. In these the degree of the response was in inverse proportion to the duration of the peritoneal soiling. The rapidity and degree of this response appear to have some prognostic significance.

In cases where the failure is "reversible" it has been our experience that this method will give a more rapid and effective response than simple infusions. Properly administered it carries with it no risk of pulmonary oedema.

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