Laparotomy was planned for undiagnosed intestinal obstruction. Following premedication (pethidine hydrochloride 50 mg.) the abdomen was opened under an "arrow-head" block (Evans, 1949) (lignocaine, 700 mg., and adrenaline, 0.3 mg.). A further 40 mg. of pethidine hydrochloride was given in intermittent doses through the intravenous drip during this period. On exploration of the peritoneal cavity it became apparent that the surgical manipulations would require supplementary anaesthesia. Thiopentone sodium (80 mg., followed by 160 mg.) was given intravenously to produce light anaesthesia. Oxygen (100%) was administered by mask and later by manual ventilation following suxamethonium (25 mg.) intravenously. "Cyclaine" (5%) was used to anaesthetize the larynx, the patient was again ventilated with oxygen, and a cuffed endotracheal tube was passed. Ventilation was continued with nitrous oxide (60%) and oxygen (40%) until spontaneous respirations returned.

During this time the patient developed transient but recurrent episodes in which he appeared pallid and pulseless. The electrocardiogram showed intermittent asystole, ventricular tachycardia, or ventricular fibrillation. A diagnosis of Stokes-Adams episodes was made. During the episodes, which lasted up to three or more minutes, and which followed each other at one- to three-minute intervals, the respirations remained of good volume, but they underwent transient depression, and a few seconds of apnoea occurred, following the return of the peripheral pulse on each occasion. During the latter part of each attack the patient's pupils became transiently dilated.

A large internal hernia was reduced and the surgery rapidly completed (40 minutes), during which time 100% oxygen was continually administered, and suxamethonium (105 mg.) injected intravenously as required for surgical relaxation. The patient was then extubated and oxygen continued by mask. The episodes persisted almost continually during surgery and post-operatively, and disappeared quite suddenly two hours and forty minutes after the onset. At the start of these incidents procaine amide (100 mg.) had been twice administered, as it was felt that the ventricular fibrillation justified this medication, but no other specific treatment was given. Later nikethamide (5 ml.) was administered and repeated, to lighten the thiopentone hypnosis, and thereafter the patient was conscious and rational between attacks. As the respiratory pattern suggested that a "chemoreceptor" drive was controlling his respirations, the oxygen which had been administered during all the attacks was withheld on two occasions. Only one further attack occurred.

The patient showed no signs of cerebral damage following these long periods of "arrest" and made an uninterrupted recovery, being discharged home on the 17th post-operative day.

Discussion

The mechanisms which may have contributed to the sudden occurrence of Stokes-Adams attacks in this patient include vagal or sympathetic overactivity, or factors concerning ventilation management.

Vagal Stimuli.—Even in the presence of complete heart-block, visceral, laryngeal, or pulmonary reflexes may have contributed to these episodes. In this respect, however, Johnstone (1955b) concludes (as a result of observations of laryngeal movements and electrocardiographic changes) that suxamethonium provides better and safer conditions for endotracheal intubation than other relaxants. In this patient, also, topical anaesthesia of the larynx was performed, and no irritant vapours were used. In spite of his conclusion, however, Johnstone has shown that a definite slowing of pulse occurs in some patients (a muscarinic acetylcholine-like effect) following the administration of suxamethonium, and in retrospect there seems very little doubt that atropine should have been included in the premedication of this patient. In one of the more severe cases reported by McLeomore and Levine (1955) atropine had also been omitted from the premedication.

Sympathetic Overactivity.—The effect of excessive adrenaline on the intact Purkinje cells may give rise to ventricular arrhythmias which may be depressed by procaine, but in this patient it seems unlikely that the adrenaline in the infiltration and block could have caused any deleterious effect, and the administration of procaine amide can be shown to be definitely contraindicated in Stokes-Adams syndrome.

Ventilatory Management.—Anoxia, which may always be a factor in the administration of an anaesthetic, and which could contribute to cardiovascular collapse, had been avoided in this instance. Conversely, it is difficult to dissociate the onset of the attacks from the administration of 100% oxygen by manual inflation. It is known that the administration of high oxygen concentrations may have a deleterious effect on the respiratory mechanism in chronic pulmonary disease associated with hypercarbia, and Stead *et al.* (1954) have shown, in animals, that sudden lowering of the alveolar carbon dioxide levels, after prolonged hypercarbia, may raise the plasma potassium to cardiotoxic levels, precipitating ventricular fibrillation. It is an interesting conjecture whether efficient ventilation with a high percentage of oxygen, to which he was unaccustomed, might not have been a factor on the onset of these attacks in this patient. There is little doubt that the episodes disappeared when manual oxygenation was withheld.

This experience brings to the fore several points of interest, particularly the differentiation between these attacks and "true" cardiac arrest. It is doubtful whether this man would have survived a thoracotomy, and it is worth noting that these patients seem to recover with little specific treatment.

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HEPARIN AND SYMPATHETIC BLOCK IN TREATMENT OF VENOUS THROMBOSIS

EXPERIMENTAL INVESTIGATIONS

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At present there are two main methods of treatment of venous thrombosis: (1) by anticoagulant agents, and especially by two main compounds of this group—heparin and dicoumarol; and (2) by paravertebral procaine block of the sympathetic system. Both methods are supported by evaluation of clinical results, but it is difficult to compare them with precision. Encouraged by Professor T. Butkiewicz, I decided to investigate this problem experimentally.

Experiments were designed to produce thrombosis and then to apply treatment either by heparin or by procaine block of the sympathetic system. The importance of experiments such as we carried out on 50 dogs may be gathered when it is realized that in the accessible medical world literature we could find no experimental work evaluating comparatively these methods of treatment.

The results of treatment of phlebothromboses were analysed with the aid of microscopical examination of excised specimens of veins affected by the thrombotic process and by phlebographic examination (the latter being the subject of a separate paper). In the Polish literature of the last 60 years I found many papers concerned with the production and treatment of thrombosis.

I. Experimental Production of Venous Thrombosis (8 Dogs)

I had first to get acquainted with the microscopical structure of the veins of normal dogs and with technical problems of the experimental production of thrombosis. On the basis of experiments described by Gruca (1928) and Ochsner and de Bakey (1941) thrombosis was produced by intravenous injections of 2.5 ml. of 50% solution of sodium salicylate. The injections were made into the saphenous vein.

Segments of veins, including the site of injection, were excised at 6, 12, 24, and 72 hours, and at 7 and 10 days after the production of thrombosis. The specimens were fixed in formol solution and sections were prepared for microscopy. Examination proved that intravenous injection of 2.5 ml. of 50% solution of sodium salicylate initiates the thrombotic process in dogs. The beginning of thrombosis was distinctly seen 12 hours after the injection, and the first symptoms of thrombosis were apparent in seven days. At later stages (7 to 10 days) the changes characteristic of hyaline degeneration of the intima were noticeable in the walls of the vessels.

II. Experimental Evaluation of Action of Heparin on Course of Thrombosis (19 Dogs)

These experiments were carried out in two groups. In the first group (10 dogs) the therapeutic action of heparin on the early stage of the thrombotic process was investigated. Heparin treatment was started six hours from the time of the intravenous injection of 50% solution of sodium salicylate and lasted 1 to 10 days. The heparin used contained 5,000 units (50 mg.) per ml. Every six hours 50 mg. was injected into the cephalic vein, 100 mg. being injected for the night. Veins were excised at intervals of 1 to 10 days from the beginning of treatment and sections were prepared.

In the second group (9 dogs) the action of heparin on more advanced stages of the thrombotic process was investigated. The treatment was begun in three dogs after 24 hours, in three after 72 hours, and in three after five days from the production of thrombosis. Heparin was given in the same amounts as in the first group of experiments over a period of 10 days regardless of the time the treatment started. Each dog in the second group received 40 ml.* (2,000 mg.) of heparin during the 10-day period.

At the end of treatment the prothrombin time was measured (in the dog in normal conditions it is 10–11 seconds).

The second group of experiments proved that heparin administered 6 to 24 hours after the injection of concentrated solutions of sodium salicylate does not prevent the production of thrombosis, which after 10 days is well organized and enters the stage of vascularization. In my experiments I could not assess the fibrinolytic action of heparin in cases in which the drug was given three days after production of thrombosis.

The following changes were noticed in microscopical pictures: (1) The contraction of vessels even when the thrombosis was absent. This sign is clearly seen in the vein of a dog owing to the strong development of smooth muscle in the venous wall. As a result of chronic contractures, extension and rupture of elastic fibres was seen. (2) The stimulation and proliferation of the intima of vessels characterized by production of endothelial finger-like papillomatous growths. (3) The presence of fragmented erythrocytes and haemosiderin granules located near the internal surface of

the veins in those dogs in which the treatment began less than six hours after the intravenous injection of sodium salicylate solution. This finding can be regarded as the beginning of the thrombotic process, not fully developed because of the therapeutic action of heparin.

III. Experimental Evaluation of Action of Paravertebral Procaine Block on Course of Thrombosis (23 Dogs)

It was necessary to study the technique of lumbar procaine block in dogs before the experimental work began. The experiments were carried out in two groups. The first comprised 14 dogs, the second 9 dogs. In the first group treatment started soon after the production of thrombosis, and procaine block was made not later than six hours from the time of injection of a 50% solution of sodium salicylate (eight experiments). In two cases treatment began 24 hours after the production of thrombosis. In four dogs procaine block started 11 days after—that is, in the late stage of the development of the thrombosis. The treatment by procaine paravertebral block was done bilaterally (with 50 ml. of 0.25% procaine each) and lasted in the early stages of thromboses for 1 to 10 days. It was shown that procaine block starting not later than six hours from the production of thrombosis was without result when one, three, or five blocks were done. In such cases the thrombosis was fully developed. In contrast, the therapeutic effect of procaine was evident in animals receiving four, six, seven, and eight procaine injections. Treatment by blocks beginning 24 hours after the production of thrombosis did not prevent its development and did not influence the microscopical appearances.

The treatment of venous thrombosis by procaine block beginning after 11 days—that is, in the late stage of its development—influenced neither the microscopical picture nor the progress of organization of the thrombosis.

In the second group (9 dogs) treatment by procaine sympathetic block started 24 and 72 hours from the production of thrombosis and in five days from the intravenous injection of the solution of sodium salicylate. Treatment lasted 10 days with bilateral lumbar procaine block done once daily.

This systematically conducted treatment, starting 24 hours, 72 hours, and 5 days after the production of thrombosis, did not result in its dispersal. Histological examination of specimens of veins in animals treated by paravertebral procaine block gave the following results: (1) the hyaline changes in the intima of vessels were seen more often than in the series of examinations on the therapeutic action of heparin; (2) absence of distinct signs of chronic contracture and the decrease in diameter of veins: such changes are, however, quite difficult to appraise by histological methods owing to the differences in size and weights of the dogs used for experiments; (3) absence of distinct proliferative changes in the intima of veins as seen in the series of dogs treated with heparin; and (4) in cases treated by paravertebral procaine block, in which the thrombosis did occur, the organization and vascularization were evident. Such changes appeared earlier and were more obvious in animals treated by procaine block than in control animals. On the other hand, the proliferation of endothelial cells was much more evident in dogs treated with heparin.

Discussion

Analysing the microscopical findings, it should be emphasized that the histological criterion can be applied to the evaluation of morphological and statistical aspects of the problem, but is inadequate for appraisal of dynamic changes in the blood supply of the extremities. Therefore the evaluation of the results of treatment of venous thrombosis by heparin and procaine block should also include the phlebographic examinations.

In six experiments carried out on dogs treated with heparin or with procaine block the prothrombin time was measured 10 days after the administration of heparin and after 10 lumbar blocks carried out over 10 days. In all these experiments the prothrombin time was not prolonged.

Conclusions

Many questions connected with the problems tackled remain unsolved; nevertheless, while further investigations are necessary it seems that the following conclusions are justified:

1. The intravenous injection of a 50% solution of sodium salicylate results in thrombosis appearing 6–12 hours later. The first evidence of organization is seen after seven days.

2. The administration of heparin, in amounts of 200 mg. daily, 6–24 hours after the production of thrombosis prevents the development of the thrombotic process.

3. Heparin treatment given three or more days after the production of thrombosis does not prevent its development. Microscopically, symptoms of the fibrinolytic action of heparin are absent.

4. Veins of dogs treated with heparin present in most cases papillomatous proliferations of the endothelium, whereas in dogs treated with procaine block the picture of hyaline degeneration of the intima is prevalent.

5. The application of procaine block less than six hours from the production of the thrombosis prevents the full development of the thrombus, provided the treatment lasts for at least four days.

6. Procaine block applied 24 or more hours after the time of the injection of sodium salicylate solution does not disperse the existing thrombus; nevertheless it accelerates organization of the thrombosis as compared with non-treated animals.

7. The degree of organization of the thrombosis in dogs treated with heparin or with procaine block is approximately the same. The proliferation of endothelial cells is more marked in thrombosis after heparin treatment.

8. The prothrombin time after 10 days of heparin or procaine block shows no significant changes from the normal.

9. The histopathological examinations are not sufficient for the evaluation of dynamic changes of blood supply of the extremity and should be supplemented by the analysis of the phlebographic appearances.

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A SALICYLSULPHONIC ACID TABLET TEST FOR PROTEIN IN URINE

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This communication describes the trial of a commercially available tablet test for protein in urine (albuminuria), which has been designed to take the place of the standard salicylsulphonic acid test. It must be emphasized, because of the common use of the term "albuminuria," that in all circumstances protein present in urine is a mixture of albumin and globulins, with albumin predominating; and this tablet test, the standard salicylsulphonic acid test, and the boiling test all detect every type of protein in urine, not albumin alone. We shall therefore only employ the term "proteinuria." Each tablet ("altest") contains about 25 mg. of salicylsulphonic acid, effervescing agents, and a trace of bromocresol green. A similar tablet called "bumintest" is marketed in the U.S.A. The latter test cannot be recommended for convenience because it entails dissolving the bumintest salicylsulphonic acid tablet in water to make a solution with which to test the urine, and we understand that bumintest is not being introduced into this country.

Method

A series of solutions of protein in urine were prepared using (1) normal human serum, (2) standard albumin solution, (3) urine from a nephrotic patient, at total protein concentrations of approximately 0.01, 0.005, 0.0025, and 0.001 g. per 100 ml. of urine. Each protein concentration was prepared in urines of approximately specific gravities 1002, 1010, and 1020, and separate samples of each were adjusted to approximate pH 5, 6, 7, and 8.

Urines containing Bence Jones protein, a high concentration of urates, and the radio-opaque substances iopanoic acid, diodone, sodium acetoazote, and "biligradin" and "urogratin" were also examined.

Each urine was tested by three methods: (1) standard "boiling test" (Harrison, 1947). (2) Standard salicylsulphonic solution test (about 5 ml. of urine plus about 0.5 ml. of salicylsulphonic acid (=125 mg.) (Harrison, 1947)—called "solution test" below. (3) altest; the method recommended by the manufacturers was found generally satisfactory—called "tablet test" below.

Urine which is cloudy should be filtered before carrying out the tablet test, as with other tests for proteinuria. An "inch" (about 4 ml.) of urine is placed in a test-tube, and one tablet added. When the tablet has dissolved completely (which takes about one minute) the tube is gently shaken, the froth is allowed to clear, and the mixture is examined. (We find, however, that the tablet dissolves more easily if the tube is continuously shaken.) The fluid should be yellow; if it is blue or green this indicates that the mixture is still alkaline, and one or more tablets are added until the final solution is acid and the fluid becomes yellow. The result is read in the same way as other tests for proteinuria: no protein—clear (yellow) solution; protein present—cloudy mixture or white precipitate, depending on the concentration of protein.