amount of arterial blood lost into the tissues during and immediately after the trauma depends on (a) the height of the arterial pressure in the ruptured vessel, and (b) the time elapsed before the haemostatic factors of arterial retraction and coagulation stem the initial extravasation.

After ligation of the main artery, and though the collateral circulation is quite effective for ordinary purposes of nutrition, etc., trauma to the limb results in extravasation of blood at only one-third of full arterial pressure (for this was the pressure discovered by direct measurement in the preceding experiments). During the time interval before haemostatic mechanisms come into action there is thus a smaller effusion of blood into the traumatized part. This, then, explains how the femoral ligature can reduce local blood loss after trauma without necessarily implying a defective collateral circulation through the limb.

As regards the toxæmic theory of shock, these observations agree with the deductions of Blalock—that shock does not result if all venous channels are open to the systemic circulation, provided that local blood loss into the limb is restricted.

These results are also consistent with those of all observers since the original Cannon-Bayliss experiment who have failed to find shock resulting from sensory-nerve stimulation under experimental conditions. How do these observations compare with those of O'Shaughnessy and Slome? It will be recalled that these workers severed all vascular connexions to the hind limb of an animal, A, and kept this limb alive by cross-circulation from a second animal, B. (It is interesting to note in parenthesis that to isolate this limb from the general circulation needed an extremely extensive multiple ligation of all collateral channels.) On traumatizing the perfused limb of animal A they were able to produce late shock in the systemic circulation of animal B. The limb was in connexion with the systemic circulation by only nervous channels. The nature of this shock must, however, be regarded with suspicion, as the necropsy appearances of the tissues which they describe are in no way consistent with their own excellent description of the typical appearances in traumatic shock. The great criticism of this elaborate experiment is that incidental trauma (which is extensive) is biased towards the production of the desired result—i.e., to produce shock. Compare this with the femoral ligature experiment, in which experimental factors are biased against the desired result—i.e., for a positive result the animal must *not* pass into shock during an experiment which is in itself very likely to result in shock. This is a very stringent experimental criterion.

In interpreting the results of the femoral ligature experiment it is possible to go a step further. There is always the theoretical possibility that traumatic shock might not be the result of only one factor, but of the combined action of several factors. Most experiments on traumatic shock have been ingeniously designed to study the action of only one factor at a time. In the experiment of femoral ligation described here all factors are capable of acting at one and the same time. Thus after losing 19% of its blood volume and being open to neurogenic and toxic shock channels, the blood pressure was still high after six hours.

Conclusions

In the cat, under chloralose anaesthesia and for periods up to six hours after severe trauma to a limb, no evidence could be found for the existence of any shock-producing factors, or combination of factors, other than that of local fluid loss.

This work was done in the physiological laboratories of King's College, London, in 1939, through the kindness of Prof. R. J. S. McDowall, to whom I am deeply indebted. The costs of the research were defrayed by a grant from the Medical Research Council.

BIBLIOGRAPHY

- Blalock, A. (1930). *Arch. Surg.*, Chicago, **20**, 959.
 — (1934). *Ibid.*, **29**, 837.
 Cannon, W. B., and Bayliss, W. M. (1919). *Med. Res. Cncl. Sp. Rep. Ser. No. 26*, London.
 Dale, H. H., and Laidlaw, P. P. (1918). *J. Physiol.*, **52**, 355.
 — and Richards, A. N. (1918). *Ibid.*, **52**, 110.
 Holt, R. L., and MacDonald, A. D. (1934). *British Medical Journal*, **1**, 1070.
 — (1935). *Proc. roy. Soc. Med.*, **28**, 1473.
 Moon, V. H. (1938). *Shock and Related Capillary Phenomena*, New York.
 O'Shaughnessy, L., and Slome, D. (1935). *Brit. J. Surg.*, **22**, 589.

DICOUMARIN IN THE TREATMENT OF PUERPERAL THROMBOSIS

BY

ALBERT DAVIS, M.D., Ch.M., F.R.C.S.

Consultant Obstetric Surgeon, London County Council

AND

MARGARET PORTER, B.Sc.

Biochemist, Dulwich Hospital (L.C.C.)

3:3-methylene-bis-(4-hydroxy-coumarin)—“dicoumarin”—for short—is the anticoagulant principle of spoiled sweet clover, ingestion of which causes haemorrhagic disease in cattle. Since its introduction by Link in 1941 the drug has been employed experimentally in a variety of conditions, notably post-operative thrombosis, and the present paper embodies the results of an investigation into its possible value in obstetrics. In all, 43 cases of post-partum thrombosis were treated. They were of every degree of severity, from small saphenous lesions to bilateral femoral blockage; but, in view of their common origin, the general action of the drug, and the homogeneity of its results, they are here grouped together without further classification.

Properties

Dicoumarin is a powerful anticoagulant, the action taking place at the prothrombin level. Given by mouth the drug takes approximately 24 hours to act, but with continued administration the result is a steady rise in the clotting time, the effect lasting for several days after the dicoumarin is discontinued. It greatly reduces the incidence and degree of thrombus formation after the intravenous injection of ethanolamine in dogs (Richard and Cortell, 1942), and is apparently similarly effective in preventing post-operative thrombophlebitis and pulmonary embolism in man (Baker, Allen, and Waugh, 1943). It also appears to limit the extension of an already established thrombosis and to produce symptomatic improvement in cases of thrombo-angiitis obliterans (Bingham *et al.*, 1943). Most observers state that although dicoumarin is an anti-prothrombin its effects are not antagonized by vitamin K. Our own results, however, show that when both preparations are administered simultaneously the coagulation-time curve rises more slowly and less steeply than when dicoumarin is given alone. This confirms Townshend and Mills's (1942) clinical observation that, while blood transfusion failed to produce any perceptible decrease in the prolonged prothrombin time of a case in which dicoumarin had induced haemorrhage, a second transfusion plus vitamin K therapy resulted in an immediate drop of the prothrombin and coagulation times to normal levels, and these normal values were maintained. It would indeed be surprising if this view of the antagonism of the two drugs were incorrect; for, theoretically, vitamin K is primarily concerned with the physiological elaboration of prothrombin in the liver. One must assume that its reported impotence in some cases of established dicoumarin haemorrhage is due to secondary changes produced by the anaemia.

Dicoumarin differs from heparin in method of administration, speed of initial response, and mode of action. The latter must be given by intravenous injection; but its action is instantaneous, the effect being produced by inhibition of platelet agglutination. Otherwise the clinical effects are similar, except that heparin haemorrhage reacts well to simple blood transfusion.

Dosage

Experimental overdosage with dicoumarin in animals produces multiple haemorrhages. In fatal cases there is central necrosis of the liver (Rose, Harris, and Chen, 1942), with widespread haemorrhage indiscriminately throughout the body. There is a considerable difference in tolerance between various species of animals, and also among individuals of the same species. This latter is of much significance, for it applies equally to man, and calls for extreme care in therapeutic administration; in fact, few of the earlier clinical reports are without a description of one or more cases of idiosyncrasy. The optimum dose is that which will reduce prothrombin to 30% of normal (Davidson and MacDonald, 1943), and this has been calculated at 200–300 mg. a day. We have taken the

higher figure, given in three separate eight-hourly doses, and as there have been no untoward results in any of our cases this dosage may be taken as reasonably safe. Published results, however, show that the margin of safety is a narrow one, apart from the possibility of idiosyncrasy, and it is essential to control the treatment by daily estimation of the prothrombin, bleeding, or clotting time. The first is the most accurate, but in our cases of already established thrombosis we have found it adequate to rely on the other two. The curves obtained parallel control prothrombin-time curves almost exactly, and their calculation is consequently easier for routine ward work.

The blood reaction to dicoumarin given in the dosage suggested is variable, but as a rule there is an average daily rise in the coagulation time of one minute, beginning 24 hours or more after the first dose. This is independent of the initial normal clotting time, which itself varies in different patients and in the same patient at different times. The time increases more or less steadily for several days, after which it remains stationary or may even be reduced, in spite of the continued ingestion of dicoumarin. The effect persists for two or three days after the drug is stopped, and the coagulation rate is usually back to normal in a fortnight. We have, however, met two striking exceptions in which the clotting time remained considerably higher than the initial normal for several months. This suggests the need for extreme care in prescribing dicoumarin for patients who have been treated with it before.

Results

The cases varied so widely in severity that it was impossible to find an exact parallel series for purposes of control, but comparison with the same number of untreated cases showed a marked improvement after dicoumarin. There were slight but definite amelioration of pain, a fairly rapid diminution of the oedema, and a shortened-average stay in hospital—19 as against 28 days.

In addition the incidence of pulmonary embolism was lowered from 9 to 4%, and in only one case was this of any degree of severity. The drug was well tolerated, and there were no untoward complications and no suggestion of spontaneous haemorrhage in any of the cases.

Conclusions

There is no doubt that dicoumarin is of value in the particular type of patient we have investigated, and in these cases of established thrombosis it would appear to be fairly safe. The freedom from haemorrhagic complications may be due to the normal increase in the coagulability of the blood during the puerperium; but whatever the factor concerned it is of significance, for ours is the only considerable series which does not contain at least one instance of dangerous bleeding, and that in spite of a fairly high dosage. But the fact that other observers have reported accidents of a serious nature so frequently in the treatment of similar conditions must necessarily modify final judgment, and there is no doubt that the drug needs extremely careful handling. We believe, however, that the results obtained justify its employment, always provided that the haematological effects are stringently controlled by daily prothrombin or coagulation-rate estimations by a skilled laboratory technician.

We are indebted to Messrs. Organon Ltd. for generous supplies of dicoumarin and to Dr. A. N. Macbeth and Mr. J. Foley for their interest and co-operation.

REFERENCES

- Baker, N. W., Allen, E. V., and Waugh, J. M. (1943). *Proc. Mayo Clin.*, **18**, 102.
 Bingham, J. B., Meyer, O. O., and Howard, B. (1943). *Amer. J. med. Sci.*, **205**, 587.
 Davidson, C. S., and MacDonald, H. (1943). *Ibid.*, **205**, 24.
 Richard, R. K., and Cortell, R. (1942). *Proc. Soc. exp. Biol.*, N.Y., **50**, 237.
 Rose, C. L., Harris, P. N., and Chen, K. K. (1942). *Ibid.*, **50**, 228.
 Townshend, S. R., and Mills, E. S. (1942). *Canad. med. Ass. J.*, **4**, 214.

R. M. Dowdeswell (*E. Afr. med. J.*, 1943, **20**, 376) examined the Widal reaction in 183 cases of typhoid fever and came to the following conclusions: (1) The rise of titre from 1 in 50 to 1 in 1,000 occurred on an average in nine to ten days; (2) the agglutinins often do not appear until after the twelfth day and may be delayed until about the twentieth day; (3) the histories of the duration of illness before admission in most cases appear to give too short a period, so that those with the later rise in agglutinins are relatively more significant.

EFFECT OF NICOTINIC ACID ON POST-OPERATIVE VOMITING

BY

WILLIAM W. MUSHIN, M.B., B.S., D.A.

AND

HELEN M. WOOD, M.B., Ch.B., B.Sc., D.A.

(From the Nuffield Department of Anaesthetics, Oxford)

The cause and prevention of post-anaesthetic nausea and vomiting are still as tantalizing and baffling a problem to us as they were to Hewitt (1893), whose words—"unfortunately our knowledge is very scanty, far scantier than it should be upon such a subject"—still apply to-day. We do know, however, some of the factors which are concerned in the production of this disagreeable feature of the recovery period. To mention but a few: a liability to vomit (e.g., travel sickness), the site of operation and the dexterity of the surgeon, the anaesthetic agent and how it is administered, and in some cases morphine, which cannot be excluded as a causal factor.

The nausea and vomiting which are a prominent feature of pellagra (Sydenstricker *et al.*, 1938), and that which occurs during sulphonamide (McGinty *et al.*, 1939) and radiation (Graham, 1939) therapy, are markedly relieved by nicotinic acid. A pilot experiment was planned to study the effect which this substance has on post-operative sickness.

Nicotinic acid is the precursor of the pellagra-preventing (P-P) factor of the vitamin B₃ group, and is the active biological group in the coenzymes I and II. It is concerned in the promotion of cell oxidation and the efficient metabolism of the cells of the gastro-intestinal tract. It has been shown that its administration increases the motility of the stomach and intestines (Crandall *et al.*, 1939).

The cases in this experiment were divided in rotation into the following three groups:—Group A: Pre-operative and post-operative—nicotinic acid 50 mg. two-hourly by mouth for two days before operation, and after operation as in Group B. Group B: Post-operative only—nicotinic acid 50 mg. two-hourly by mouth as soon as conscious, and this routine continued until nausea and vomiting ceased. Group C: Control group.

Premedication consisted of morphine gr. 1/6 and atropine gr. 1/100. The patients were anaesthetized as follows. A small dose of pentothal (0.2 to 0.3 g.) was given to produce unconsciousness, and this was followed by ethyl chloride, and then ether and air from an Oxford vaporizer. The anaesthetics were all administered by the same anaesthetist. In the recovery period morphine was given if the patient was in pain or was restless. The operations were routine hospital lists, and if any bias was shown in their selection it was in the direction of abdominal operations. None of the operations were emergencies.

It is difficult to assess the disability of a patient due to nausea or vomiting. We felt that, rough measure though it might seem, an accurate impression is conveyed in terms of bouts of vomiting.

TABLE I

	Nicotinic Acid	Total	Did not Vomit	1 to 3 Bouts of Vomiting	Over 4 Bouts of Vomiting
Group A	Pre- and post-operative administration (750-900 mg. per patient)	29	10	11	8
Group B	Post-operative administration only (300-500 mg. per patient)	30	7	15	8
Group C	Control	30	6	15	9
	Totals	89	23	41	25

On the basis of these figures the χ^2 test shows the difference due to nicotinic acid to be statistically insignificant.

Table II is a rearrangement and simplification of Table I to show the difference between those to whom nicotinic acid was given and the control group.

The χ^2 test (with Yates's correction) shows no significant difference due to nicotinic acid. However, in those who had been given nicotinic acid there is a slight trend in the direction