ANTICOAGULANTS AND ARTERIOSCLEROSIS

By KEITH BALL, M.D., M.R.C.P.

Assistant Physician, Central Middlesex Hospital

Arterial thrombosis is nearly always the cause of the final obstruction in arteriosclerosis (a term here used as synonymous with atherosclerosis or arteriosclerosis obliterans). It is thus a most important and often lethal event in the course of the patient's disease. Thrombosis may be the reaction of the blood to the ragged atheromatous protrusion which has already caused partial arterial occlusion. Yet some think that there may be a more fundamental relationship between blood clotting and atheroma formation. Duguid (1954) has suggested that the very development of atheroma is the result of repeated deposition of fibrin thrombi on to the arterial endothelium. On the other hand, the work of Morris (1952) indicates that thrombosis and atheroma may not be directly related. He found that although there had been a sevenfold increase from 1907-14 to 1944-49 in the number of cases of coronary heart disease coming to necropsy at the London Hospital, there appeared to have been a substantial decrease of advanced atheroma in the population as a whole over this period. The relationship of dietary fat to thrombosis and atheroma is arousing considerable interest today. In Norway during the last war there was a reduction in the incidence both of cardiovascular deaths and of post-operative thrombosis at a time when fat-consumption was markedly reduced (Closs and Dedichen, 1949). Fullerton and his colleagues (1953) showed that the lipaemia after a fatty meal increased the coagulability of the blood.

Whatever the true relationship between thrombosis and arteriosclerosis, the anticoagulants have an important place in the treatment of arteriosclerotic disease. Their chief use follows an acute arterial thrombosis whether of the coronary or the peripheral vessels. But in patients with recurrent arterial occlusions, their long-term use may prove well worth while.

Myocardial Infarction

Anticoagulants have been used in the treatment of myocardial infarction for nearly ten years, yet there are still many different opinions concerning

their true value. On the one hand, Wright and his colleagues (1954) maintain that their use improves the prognosis in every patient who has had an infarction. Yet on the other hand, Evans (1954) considers this treatment unjustified and dangerous. Between these extremes lie the moderates who see indications for their use in selected cases.

Wright bases his views on the findings of a committee of the American Heart Association which investigated 1,031 cases of cardiac infarction treated in several hospitals; 589 patients were treated with anticoagulants and were compared with 442 patients treated on conventional lines. Twenty-six per cent. of the control group developed thrombo-embolic complications compared with 11 per cent. of the treated group. 23.4 per cent. died in the control group as against 16.0 per cent. in the treated group. Tulloch and Gilchrist (1950) arrived at similar conclusions. In a carefully controlled clinical trial they found that anticoagulants reduced the rate of thrombotic complications from 26 per cent. to 10 per cent. and the mortality from 42.2 per cent. to 19.5 per cent. Both Wright and Gilchrist believe that anticoagulants should be given in every case, since they feel that the patient's course cannot be predicted from his condition at the outset of the disease.

Evans bases his condemnation of the treatment on several grounds. He found that in eight post-mortem investigations in which a total of 2,451 cases were examined, only 43 per cent. were found to have thrombosis in the coronary circulation. He also records the mortality rate in several different series of patients with cardiac infarction, noting that his own rate of 19 per cent. compared favourably with that of several groups treated with anticoagulants (although there are obvious fallacies in comparing mortality rates at different hospitals).

Russek and Zohman (1954) believe in a middle-way, the conservative treatment of the 'good-risk' case, reserving anticoagulants for those who present one or more of the following features: previous myocardial infarction, intractable pain,

extreme or persistent shock, significant cardiac enlargement, gallop rhythm, congestive heart failure, cardiac arrhythmia, diabetic acidosis, marked obesity, previous pulmonary embolism, varicose veins, thrombophlebitis or polycythaemia. In this series the patient was placed in the good-risk category on the day of admission. This was done in order to be able to counter the criticism of Wright who maintains that it is only possible to diagnose a good-risk patient in retrospect since the disease runs such an unpredictable course; 122 (46 per cent.) out of 271 cases of myocardial infarction were considered to be good-risks. Six of the 122 died, including three within the first 48 hours. It is argued that only one death might have been prevented by the use of anticoagulants in this group. In their view, the risks of haemorrhage outweigh any advantage to be gained from the use of anticoagulants in the good-risk patient. Littman (1952), another moderate, believes that anticoagulants should be reserved for patients with congestive heart failure, prolonged shock, intractable pain or high fever. Papp and Shirley Smith (1951) found that anticoagulants were unnecessary in the treatment of slight and moderate cases of myocardial infarction, where the mortality was less than 2 per cent. They confirmed the value of the treatment in severely ill patients.

The problem of deciding which cases to treat must also be related to (a) the risks of treatment, and (b) the availability of a bed in a hospital where the treatment can be adequately controlled. The risk of haemorrhage depends largely on the care with which the treatment is supervised. When the drugs are used by experienced physicians and prothrombin estimations are made by reliable methods, the risks are certainly small. Nevertheless, Russek found, on circulating 229 physicians who had used anticoagulants, that 122 deaths from bleeding had been observed, showing that this risk can never be neglected.

From the Registrar-General's Statistical Review (1949) it has been estimated that in England and Wales not more than one-fifth of the deaths from coronary disease occur in hospital, and it is probable that the proportion of patients admitted to hospital for treatment of this condition is equally small. Thus only a minority of patients, who have myocardial infarctions, at present receive hospital treatment. Until many more hospital beds become available, or until domiciliary anticoagulant treatment becomes practicable, it is reasonable to select for admission those patients who are likely to obtain the greatest benefit from specific therapy.

What then is a reasonable policy in the present circumstances? Patients with first attacks who

are under 60 and who do not have congestive failure, shock, or other serious complicating factors, should be treated at home if conditions there permit. Other patients should be admitted to hospital, where active treatment for shock and arrhythmia may be required apart from the anticoagulants. There is a great need for a safe anticoagulant which can be administered in the home. At present none exists, and home treatment with the coumarin type of drugs should not be given unless there are facilities for daily prothrombin estimations. Intramuscular heparin can be given to severely ill patients who cannot be admitted to hospital (*vide infra*).

Acute Coronary Insufficiency

For some time it has been recognized that there is a state of myocardial ischaemia intermediate between angina of effort and myocardial infarction, and it has been called acute coronary insufficiency. This condition often precedes actual infarction. Mounsey (1951) showed that 29 per cent. of patients with infarction gave a history of progressively increasing angina prior to the attack. These symptoms are probably due to the progressive development of a thrombus in a coronary artery. If this process could be halted, infarction should be prevented. Nichol (1954) gave anticoagulants to 177 patients with acute coronary insufficiency and maintained them on long-term treatment. Twenty-seven patients stopped treatment after 7 to 60 days and 8 of them succumbed to an acute coronary attack within another 30 days. Only 4 of the 146 patients remaining on long-term treatment died from acute infarction.

This indicates that anticoagulants should be given when there is a history of angina of rapidly increasing intensity, despite the absence of evidence of infarction. They should be given for at least three to four weeks, and Nichol's results suggest that the patient's outlook would be considerably improved by continuing the treatment indefinitely.

Acute Peripheral Arterial Occlusion

In patients with peripheral arteriosclerotic disease, deterioration results from recurring incidents of arterial thrombosis. The site of the resultant occlusion and the state of the collateral circulation determine the extent of the damage. On the one hand, the distance the patient can walk without leg pain may be slightly shortened. But on the other, the picture of acute arterial occlusion may supervene, the life of the limb being in immediate danger. In this case treatment must be swift. Anticoagulants are essential in order to prevent spread of the clot to other parts of the arterial tree with occlusion of the collateral chan-

Drug	Initial dosage		Average daily maintenance dosage	Number of doses daily	Maximal therapeutic effect	Maximal duration of effect
	1st day	2nd day				
Dicoumarol	mg. 300	mg. 200	mg. 50-150	One	36-72 hrs.	7 days
Ethyl biscoumacetate	1,200	900	450-600	Three	24-36 hrs.	48-72 hrs.
Phenylindanedione	200	100	50-150	Two	24-36 hrs.	48-72 hrs.

nels. Every doctor should carry heparin for such an emergency. Apart from its immediate anti-coagulant effect, it has been shown to increase the peripheral blood flow.

Wright and her colleagues (1953) investigated the effect of anticoagulants on artificially produced thrombosis in the femoral arteries of rabbits. The time taken for recanalization was recorded by arteriography. The group treated with ethyl biscoumacetate (Tromexan) showed an average recanalization period of $3\frac{1}{2}$ weeks, while the controls were still occluded after several months. This work suggests that arterial recanalization may occur in man following the use of anti-coagulants, and is another reason for their use. It has certainly been noted following embolic occlusion, but is less likely to occur where the thrombus results from arteriosclerosis.

Practical Administration of the Anticoagulant Drugs

Heparin remains the drug of choice where an immediate effect is needed and it should be given in every thrombo-embolic emergency until one of the coumarin type of drugs has taken effect; 100 mg. (10,000 i.u.) should be given intravenously every 4-6 hours. It is the only anti-coagulant that can be given safely without laboratory control and thus can be used in the home, although frequent intravenous injections are obviously impracticable for the general practitioner. Insertion of a Gordh needle (an indwelling intravenous needle with a rubber diaphragm) may allow repeated injections for a few days, but it is rarely possible for prolonged use.

Intramuscular heparin is less satisfactory, but should be given where there are no other facilities. Wynn and Goodwin (1952) found that when 150 mg. was given intramuscularly in a strength of 250 mg. per ml., the maximum effect occurred in 3-4 hours and that the clotting time was maintained at more than twice normal for 9-10 hours. Local reactions were minimized when the heparin was mixed with 1-2 ml. of 1 per cent. procaine and when firm pressure was applied at the site of injection. Twelve-hourly injections were given.

Despite these precautions, the development of haematomata prevented continued treatment in a quarter of their patients. Raaschou (1954) and his colleagues found that 300 mg. of a concentrated solution could be given subcutaneously twice daily without severe reactions.

The coumarin type of drugs and phenylindanedione (Dindevan, Indema) can rarely be used outside hospital, since daily prothrombin estimations are essential. The above table compares the characteristics of the three most commonly used drugs.

With care any of these drugs can be safely and effectively used. Ethyl biscoumacetate is much more expensive than the other two and its routine use hardly seems justified. Severe haemorrhage usually results from lack of accurate daily prothrombin estimations, from inexperience in the use of the drug employed, or from treating unsuitable patients. Patients with severe kidney or liver disease and those with a liability to bleed from granulating areas should not be given anti-coagulant therapy, while severely ill or shocked patients need smaller doses.

Phenylindanedione has certain advantages over the other two. There is much less cumulative effect than with dicoumarol, yet its rather longer action makes steady control easier than with ethyl biscoumacetate. Toohey (1953) found that an adequate therapeutic prothrombin level was attained in 48 hours from the onset of treatment in 62 out of 68 patients. He aimed at a level of 10-20 per cent., yet found no case of haemorrhage in the series. He gave 100 mg. of the drug twice on the first day and 50 mg. twice on the second day. Coon and his colleagues (1953) compared the effects of dicoumarol, ethyl biscoumacetate and phenylindanedione. They gave rather larger doses of phenylindanedione than usual, i.e. 300 mg. followed by a further 300 mg. in 12 hours and 100 mg. 12 hours later, and found that 95 per cent. of their patients reached a therapeutic prothrombin level within 48 hours. The incidence of bleeding (6.5 per cent.) was less than with ethyl biscoumacetate (9.0 per cent.) and dicoumarol (11.2 per cent.).

A pinkish-orange colour may develop in the urine and Coon noticed a temporary albuminuria lasting a few days. The most serious toxic effect so far described is agranulocytosis. Brown and MacMillan (1954) noted two cases out of 261 patients treated, one of whom died. Townsend and his colleagues (1953) reported that one patient out of 115 so treated developed agranulocytopenia which recovered completely when phenylindanedione was withheld. Kirkeby (1954) records the case of a man of 55 who developed agranulocytosis after five weeks' treatment with phenylindanedione for cardiac infarction. A leucocytosis developed after he was given cortisone, but he later died from uraemia of unknown cause. These four case-reports show that when phenylindanedione is used a careful watch should be kept for this complication and that the drug should be stopped directly a rash or sore throat appears.

The newer longer acting preparations, such as cyclocumarol and 3-(1'-phenyl propyl)-4-hydroxycoumarin (Marcoumar) may become more widely used, now that in Vitamin K₁ an effective antidote to the coumarin drugs has been found. Marcoumar is being used especially on the Continent, the reported incidence of haemorrhage being low (Koller and Jacob, 1953).

Long-term Therapy

Preventing thrombosis is certainly better than treating it and for this purpose anticoagulants can be given over long periods to out-patients provided there are proper safeguards. The main indications are recurrent thrombophlebitis, rheumatic heart disease with emboli, cardiac infarction and peripheral arterial thrombosis. After the patient has been stabilized on one of the coumarin type of drugs he is discharged on a maintenance dose. His prothrombin level is tested every week, or later every fortnight if it remains steady, and an attempt is made to keep it between 25 per cent. and 40 per cent. When the result is known, a card is sent to the patient indicating the daily dose of the drug for the following week. Only patients who can be relied upon to co-operate intelligently should be given long-term treatment. They can be supplied with Vitamin K₁ 10-20 mg. to be taken at the first sign of bleeding, when they should immediately report to the hospital.

Tulloch and Wright treated 227 patients with various thrombotic conditions for a total of 180 years. Of these, 32 patients with myocardial infarction or ischaemia received a total of 38 years' treatment. During this period two further attacks of myocardial infarction occurred. One death from haemorrhage occurred in the whole series. They concluded that out-patient long-term treatment was relatively safe and lessened the incidence

of thrombo-embolic episodes. Keyes and his colleagues (1953) compared the outlook of an untreated group of patients who had survived an infarction with a similar group treated with prolonged anticoagulants. They found that the death rate was about four times greater for the untreated than for the treated group. A carefully controlled trial over a long period is needed to show whether anticoagulants are of real value in preventing recurrences of cardiac infarction, but in the meanwhile there are good reasons to submit suitable patients with recurrent infarctions to this treatment, provided the above safeguards are carried out.

Vitamin K

The risk of serious haemorrhage during treatment with the coumarin-type of anticoagulants has been considerably reduced since the advent of Vitamin K₁. Douglas and Brown (1952) demonstrated its superiority over other Vitamin K preparations. Toohey (1954) showed that Vitamin K₁ in oral doses of 5 to 50 mg. completely restored the blood prothrombin to a safe level in 68 out of 70 patients on anticoagulant therapy. He stressed the importance of not giving an excessive dose, since bleeding might be replaced by thrombosis. Larger doses (25 to 50 mg.) should be given when there is severe bleeding, when the long-acting anticoagulants such as dicoumarol and cyclocumarol are used and when treatment is being stopped. Smaller doses (5 to 15 mg.) should be reserved for those with a dangerously low prothrombin level, but with no evidence of bleeding, when the short-acting drugs are being used and where treatment is being continued. Hilden and Munck (1953) showed that oral Vitamin K₁ was equally effective against dicoumarol, tromexan or phenylindanedione. Following treatment with Vitamin K₁ resistance to the coumarin drugs may develop. Heparin can be used until their effect has worn off. An emulsion of Vitamin K₁ for intravenous use has recently become available (Mephyton, Merck), but the oral route is likely to prove adequate unless the haemorrhage is very severe or the patient is vomiting. A transfusion of fresh blood should be given if the bleeding is not quickly controlled.

Conclusions

The anticoagulant drugs have become indispensable in the management of most cases of acute myocardial infarction. Recent experience suggests that they also have a place in the treatment of the premonitory signs of infarction as well as in the long-term prophylaxis against recurrent attacks.

Bibliography continued on page 139

Future Problems

Three main problems remain to be solved. Infection is no longer a menace, principles of technique have been generally established and the selection of cases has been clarified by increased experience.

But the problem of vascularization and oedema causing early or late opacification of the graft is still unsolved; the solution will more likely be found in the laboratory than in the operating theatre.

Closely associated is the best method of storing donor material for on this depends the whole future of the organization and expansion of corneal graft surgery.

Mr. Gordon Clemetson of the Photographic

Unit, Queen Victoria Hospital, East Grinstead, has kindly provided the photographs.

Acknowledgments

Figs. 1 and 3, reproduced by kind permission of Messrs. Butterworth, and Fig. 2 by kind permission of The Medical Press.

REFERENCES

1. V. HIPPEL (1888), *Gf. Arch.*, **34**, 108.
2. ZIRM, E. (1905), *Arch. Ophth.*, **64**, 580.
3. POLGE, G., PARKES, A. S., and SMITH, A. U. (1949), *Nature, Lond.*, **164**, 666.
4. EASTCOTT, H. H. G., *et al.* (1954), *Lancet*, Jan. 30, 6805.
5. BILLINGHAM, R. E. (1953), 'Preservation and Transplantation of normal tissues' (Ciba Foundation), p. 218.
6. TOWNLEY PATON, R. (1953), *Trans. Amer. Ophth. Society*, **51**.
7. DE WECKER (1879), 'Ocular Therapeutics,' London, p. 145.

HOW TO GET THERE

An Address Book for the Medical profession, showing how to reach the various Colleges, Societies, Institutes and Hospitals in or near London

New (Fourth) Edition: 1954

Price 2s. 6d. (2s. 9d., post free)

Published by the

FELLOWSHIP OF POSTGRADUATE MEDICINE

60 Portland Place, London, W.1

Bibliography continued from page 129—Keith Ball, M.D., M.R.C.P.

BIBLIOGRAPHY

- BROWN, K. W. G., and MACMILLAN, R. L. (1954), *Amer. J. Med. Sci.*, **227**, 526.
- CLOSS, K., and DEDICHEN, J. (1949), *Lancet*, **ii**, 1242.
- COON, W. W., DUFF, I. F., HODGSON, P. E., and DENNIS, E. W. (1953), *Ann. Surg.*, **138**, 467.
- DUGUID, J. B. (1954), *Lancet*, **i**, 891.
- DOUGLAS, A. S., and BROWN, A. (1952), *Brit. med. J.*, **i**, 412.
- EVANS, W. (1954), *Proc. Roy. Soc. Med.*, **47**, 318.
- FULLERTON, H. W., DAVIE, W. J. A., and ANASTASOPOULOS, G. (1953), *Brit. med. J.*, **ii**, 250.
- HILDEN, T., and MUNCK, O. (1953), *Ugeskr. Laeg.*, **116**, 288.
- KEYES, J. W., DRAKE, E. H., JAMES, T. N., and SMITH, F. J. (1953), *Amer. J. Med. Sci.*, **226**, 607.
- KIRKEBY, K. (1954), *Lancet*, **ii**, 580.
- KOLLEBY, F., and JAKOB, H. (1953), *Schweiz. med. Wschr.*, **83**, 476.
- LITTMAN, D. (1952), *New Engl. J. Med.*, **247**, 205.
- MORRIS, J. W. (1951), *Lancet*, **i**, 1 and 69.
- MOUNSEY, P. (1951), *Brit. Heart J.*, **13**, 215.

- NICHOL, E. S., PHILLIPS, W. C., and JENKINS, V. E. (1954), *Med. Clin. North. Amer.*, March, 399.
- PAPP, C., and SMITH, K. S. (1951), *Brit. med. J.*, **i**, 1471.
- RAASCHOU, F., REFN, I., and VESTERGAARD, L. (1954), *Ugeskr. Laeg.*, **116**, 281.
- REGISTRAR-GENERAL'S STATISTICAL REVIEW (1949), Supplement on Hospital In-patient Statistics, H.M. Stationery Office, 1954.
- RUSSEK, H. I. and ZOHMAN, B. D. (1954), *Amer. J. Med. Sci.*, **228**, 133.
- TOOHEY, M. (1953), *Brit. med. J.*, **i**, 650.
- TOOHEY, M. (1954), *Brit. med. J.*, **i**, 1020.
- TOWNSEND, S. R., FAY, K. J., DOWNING, J. R., LAING, R., and CAMERON, D. G. (1953), *Canad. med. Assoc. J.*, **29**, 149.
- TULLOCH, J. A., and GILCHRIST, A. R. (1950), *Brit. med. J.*, **ii**, 965.
- WRIGHT, H. P., KUBIK, M. M., and HAYDEN, M. (1953), *Brit. med. J.*, **i**, 1021.
- WRIGHT, I. S., BECK, D. F., and MARPLE, C. D. (1954), *Lancet*, **i**, 92.
- WYNN, A., and GOODWIN, J. F. (1952), *Brit. med. J.*, **ii**, 893.