

day, his dizziness disappeared in a week, and after more than thirteen months the discharge has not recurred, his hearing is greatly improved, and his dizziness has ceased.

I write in order to refute the claim that four-hourly injections are necessary, as stated by Mr. I. Simson Hall (Dec. 27, 1947, p. 1050), and also to make a strong appeal to other doctors to try treating the chronic cases of otitis media with large doses of penicillin, as suggested above, since the number of cases of otitis media in the country must be enormous, and apart from the inconvenience of discharging ears and deafness there is always a danger of more serious complications. Operation, apart from its risk, is not always effective, and patients are usually reluctant to submit to it.—I am, etc.,

Sheffield, 5.

I. GOTTLIEB.

Dicoumarol

SIR.—From the vast literature on the pharmacological action and therapeutic use of dicoumarol there appear several findings which are of importance in the control of dicoumarol therapy: (a) It is not advisable to reduce the prothrombin to such a degree that the ordinary blood-clotting time becomes prolonged.¹ (b) Very low prothrombin concentrations must be attained before the clotting time is significantly altered.² (c) Intravascular thrombosis rarely occurs in patients on dicoumarol if the prothrombin is kept below 30%, while haemorrhagic complications are rare if the prothrombin is kept above 10%.³ (d) In the Quick method of prothrombin estimation the source of thromboplastin is acetone-dried rabbit brain.^{4,5}

The clotting time (Lee and White method), which Dr. M. J. Pivawer (Dec. 6, 1947, p. 928) recommends as a means of controlling the dosage of dicoumarol, has very little experimental evidence to support it. From my own experience the clotting time does not appear to give sufficient warning of the approach of, nor in some cases the arrival at, the danger level of 10% prothrombin. This is illustrated in the following case.

Case 1.—A post-operative patient received 650 mg. dicoumarol over a period of three days. On the fourth day the prothrombin concentration was found to be less than 10% by the Quick method and 35% by the Fullerton modification⁶ of the Quick method. The patient developed a haematoma at the site of operation. At this stage the clotting time (Lee and White method) was normal and no different from the clotting time estimated before the administration of dicoumarol.

Full details of Quick's method are to be found in his excellent monograph. I have found acetone-dried human brain to give as satisfactory results as acetone-dried rabbit brain. For every batch of dried brain which one obtains a graph must be plotted correlating prothrombin times with prothrombin concentrations. In the Fullerton modification⁶ of the Quick method Russell-viper venom is the source of thromboplastin. The results are often misleading and may cause an overdosage with dicoumarol. This is illustrated by the following case.

Case 2.—A post-operative case which developed a thrombophlebitis received 1,700 mg. of dicoumarol over a period of eight days. Prothrombin estimations were carried out daily by the Fullerton modification. At no time during the eight days was the prothrombin found to be below 25%, which, in view of the large amount of drug administered, was rather curious. On the eighth day I estimated the prothrombin by both methods. The prothrombin was well below 10% by Quick's method and about 25% by the Fullerton modification. Treatment with dicoumarol was immediately stopped, but the prothrombin concentration continued to fall. Six days later the patient had a severe epistaxis, and it was noticed that his operation scar was not healing. At this stage the prothrombin was less than 5% (Quick method) and about 20% (Fullerton modification). Fortunately in this case the prothrombin began to increase the next day and bleeding stopped. About six days elapsed before the prothrombin was over 30%.

Dr. Frank Marsh (Dec. 20, 1947, p. 1009) advocates a method in which "perfectly fresh viper venom of (if possible) guaranteed potency" is required. This method, in which "it may be necessary to do twelve tests on one specimen of plasma," seems to me to be complicating the issue. With the Quick method the results are so concordant that it is rarely necessary to use more than three tubes per specimen of plasma.

My conclusions are, therefore, that the most reliable method at present for the control of dicoumarol therapy is the daily

estimation of prothrombin concentration (sometimes called prothrombin activity) by means of Quick's method, in which the source of thromboplastin is acetone-dried brain. Using this method I find that 24 hours after the administration of 300 mg. dicoumarol the majority of cases show a prothrombin concentration of 50% or lower. It is these latter figures which determine the dose to be given on the second day. Most workers will agree with your correspondents that heparin is most valuable. In certain cases, during the period when dicoumarol has not yet lowered the prothrombin concentration to the optimum range of 10 to 30%.—I am, etc.,

Manchester.

H. LEMPERT.

REFERENCES

- 1 Bingham, J. B., Meyer, O. O., Pohle, F. J., *Amer. J. med. Sci.*, 1941, **202**, 563.
- 2 Davidson, C. S., and Macdonald, H., *ibid.*, 1943, **205**, 24.
- 3 Allen, E. V., *J. Amer. med. Ass.*, 1947, **134**, 323.
- 4 Quick, A. J., *ibid.*, 1938, **110**, 1658.
- 5 ———, *The Haemorrhagic Diseases*, Springfield, Illinois, U.S.A., 1942.
- 6 Fullerton, H. W., *Lancet*, 1940, **2**, 195.

SIR.—We have been interested in the increasing correspondence regarding the administration of dicoumarol and feel that the letter of Dr. M. J. Pivawer (Dec. 6, 1947, p. 928) calls for critical comment. First, in our experience Quick's method of prothrombin-time estimation has given satisfactory results. There are one or two practical points which are of importance. The blood required for the test should be withdrawn at the same time each day, preferably before a meal, and the time and timing of each stage of the technique should be consistent throughout. It is imperative that clean and smooth test-tubes be used for the test. We have found that the "stypven" solution (thrombokinase) requires renewal every third day, and if a new solution is made up from the same batch and overlapped with the old solution errors from this source are eliminated. We have found the first appearance of granularity to be a reliable end-point of the reaction. We have investigated the usefulness of the lecithin-accelerated method of Witts and Hobson, and, although impressed at first by the sharpness of the end-point, we now believe that this advantage is offset by the shortness of the actual time measured and the possible disadvantage of introducing one more variable reagent.

Unexpected minor variations of prothrombin time do sometimes occur during dicoumarol administration, but we have found that by graphing the daily results and by intelligent anticipation it is possible to maintain a patient in the therapeutic range with safety. The dosage we have employed has been 300 mg. of dicoumarol on the first day, and 200 mg. on the next two days, followed by 100 mg. daily as indicated by prothrombin time. We aim to keep the prothrombin time between two and two and a half times the result determined before therapy is begun.

Secondly, we would strongly deprecate attempts to treat patients in any circumstances which do not permit of accurate daily prothrombin-time estimation. It is generally agreed that the effect of dicoumarol on the coagulation time is less consistent than the effect on the prothrombin time. Indeed, lengthening of the coagulation time is usually not seen until quite marked increase in the prothrombin time has occurred.

Thirdly, the object of dicoumarol therapy is to prevent intravascular clotting, and if therapy is to be fully effective the coagulability of the blood must not be allowed to return to normal during the treatment.—We are, etc.,

London, E.C.1.

G. CANTI.

D. J. ROBERTSON.

German Tropical Medicine

SIR.—I want to make a comment to the leading article, "German Tropical Medicine," in the *Journal* of Nov. 1, 1947 (p. 697). You write: "Bacillary dysentery caused much trouble, particularly in Poland in 1939 and in North Africa. Treatment by sulphonamides, especially sulphapyridine, was eventually introduced, although much later than in the Allied forces."

If there is the implication that Austrian and German literature, as we are using the same language, are taken together, this statement is not correct. In fact I used "protosil" for the treatment of bacillary dysentery much earlier than the Allied forces (see Gorlitzer, V., *Schweiz. med. Wschr.*, 1940, **70**, 281; Gorlitzer, V., *Klin. Med., Wien*, 1947, **2**, 862).—I am, etc.,

New Delhi.

V. GORLITZER.