in visual acuity would result. The easing or abolition of headache for as long as several days surprised us, as the effect of the drug on the blood pressure is short-lived, lasting from a few minutes to at most an hour or two. We therefore substituted control injections of saline, elaborate and lengthy readings of blood pressure being taken as before, retinae and pupils being examined every few minutes. Equally satisfactory results in improvement in vision and lessening of headache were reported by the patients after such "dummy" injections.

Apart from this small group where improvement was effected by suggestion no really satisfactory results were obtained with the drug, and the high hopes we held for its being useful in treatment of hypertensive patients unsuitable for sympathectomy have not been fulfilled. We have found the effect of the drug on skin temperature of the extremities variable and erratic and less satisfactory than simpler methods. In some cases little or no drop in blood pressure resulted, though most patients had some depression of systolic and diastolic pressure for 3 to 30 minutes after intravenous injection of 100-600 mg. of the drug. The rate of the injection appeared to play a part as well as the dosage given, the more rapid the administration of the drug the more the effect on the blood pressure.

As stated in your annotation, T.E.A.B. is an impracticable therapeutic agent, but it may prove of use to the research worker. We have not found it a useful drug either in testing rises in peripheral skin temperature or in lessening symptoms in hypertensive subjects. In the last group of cases the psychogenic element features largely in so many cases, and it is easy to produce symptomatic relief by suggestion backed by elaborate investigation. Nevertheless it is possible that new uses may yet be found for this drug, and our trial is still in progress.—I am, etc.,

London, S.W.1.

F. DUDLEY HART.

Acute Non-specific Gastro-enteritis

SIR,—We note with interest the letter from Dr. William Forster (Dec. 13, 1947, p. 971) describing an outbreak of acute non-specific gastro-enteritis in a mental hospital, and we would like to comment on a few of the points made in it.

Treatment and Prophylaxis with Sulphonamide Drugs.—In our experience of a number of outbreaks, some in mental hospitals, treatment of established cases of gastro-enteritis of this type with sulphaguanidine has been without effect on the duration and severity of illness as compared with controls treated symptomatically, a finding in agreement with that obtained by Dr. Forster, using phthalylsulphathiazole. Dr. Forster suggests, however, that "sulphonamides were effective in prophylaxis." Examination of the data given in his letter yields little to support this conclusion, for the drugs were administered when the ward outbreaks had been in progress for some days (9-17 days) and when the attack rates were declining naturally. Again, at least four patients commenced the disease while they were actually receiving prophylactic sulphonamide.

In our experience the duration of outbreaks in mental-hospital wards where no prophylaxis had been undertaken was relatively short, due possibly to the rapid spread of the disease through an unchanging population. Thus in a Leicester mental-hospital outbreak¹ the duration of ward outbreaks on the male side of the hospital ranged from 7 to 14 days (mean 9.8 days) and on the female side from 12 to 22 days (mean 18.4 days). There was therefore considerable variation between wards, but the figures are of the same order as those (12, 15, and 20 days) occurring in Dr. Forster's wards in which prophylaxis was undertaken. The variability between untreated wards makes deductions concerning the value of prophylactic treatment extremely hazardous.

Variation in Attack Rates in Wards with Different Populations.—It was very interesting to note the uniform gradation of the size of attack rate in different wards as given in the table of Dr. Forster's letter. Thus, wards having overcrowded low-grade mental patients tended to have higher attack rates than the wards which were less crowded and had patients of a higher mental grade. We have observed a similar gradation in two mental-hospital outbreaks.^{1,2} This may be partly a reflection of the degree of day-time dispersion in different ward populations, but investigation of these differences and their relation to the mode of spread of the disease might be illuminating. The problem might be approached by comparing the attack rates in "non-specific gastro-enteritis" in these varying ward populations with the rates observed on the one hand in diseases whose method of spread is intestinal-oral, such as bacillary dysentery, or on the other hand "airborne," such as influenza.

Mode of Spread of the Disease.—In the mental-hospital outbreaks that we have investigated, as in that investigated by Dr. Forster,

case-to-case infection rather than water or massive food-borne infection has been the pattern of spread. Dr. Forster states, however, that the infection was "probably airborne" in his outbreak. It would be interesting to know the facts which led Dr. Forster to this conclusion. It is a commonly held belief that the disease is spread by the "airborne" route, but we are in ignorance of the epidemiological method which enables a distinction to be made between "airborne" and case-to-case contact spread of infection. The mere fact that the disease is very infectious, has high attack rates and a particular seasonal incidence, is not by itself sufficient evidence for a respiratory mode of spread.

The findings of Reimann *et al.*,³ who transmitted a similar gastro-enteritis to student volunteers when they inhaled nebulized filtrates of throat washings or stool but failed to infect volunteers by feeding stool filtrate, have influenced the interpretation of outbreaks in this country. Reimann was, however, the first to point out that his experiments were undertaken under difficult circumstances in that the volunteers could not be isolated from the rest of the student body which was experiencing natural attacks of the disease. Further, examination of his figures reveals that the incubation period was between 9 and 21 days in 42% of the volunteers having gastro-enteritis, and as the natural incubation period is 3-5 days it is questionable whether these later cases were in fact due to inoculation. The volunteers were inoculated in batches on six different days using, from (presumably) different donors, material which consequently may have been of different activity. The results obtained by Reimann should, therefore, be applied with caution until they have been confirmed.

Recently a well-planned and controlled experiment has been undertaken in New York by Gordon and colleagues.⁴ These investigators, using known susceptible and carefully isolated volunteers, have shown that a clinically similar gastro-enteritis of the type under discussion can be transmitted by ingestion of filtered stool or unfiltered throat washings but not by the inhalation of nebulized throat washings known to be infective by ingestion. It remains to be proved, of course, that the disease described by Reimann, the New York workers, and various investigators in this country is in fact the same regardless of the similarity of clinical picture, but enough has been said to illustrate the need for caution in labelling the disease an "airborne" infection.—We are, etc.,

B. P. MARMION.
G. T. COOK.

¹ ² These data are quoted with the kind permission of Dr. K. K. Drury, Carlton Hayes Mental Hospital, Narborough, and Dr. T. W. Davidson, City Mental Hospital, Humberstone, Leicester.

³ *Proc. Soc. exp. Biol.*, N.Y., 1945, 59, 8.

⁴ *J. exp. Med.*, 1947, 88, 409.

Penicillin in Otitis Media

SIR,—With reference to the report of the meeting of the Section of Otolaryngology of the Royal Society of Medicine (Dec. 27, 1947, p. 1049) may I be permitted to give a general practitioner's experience in the treatment of otitis media with systemic penicillin, both in acute and chronic cases?

I use the oil-wax suspension of 1,250,000 units in 10 ml., giving a single injection of 200,000 to 300,000 units daily. I had eleven cases of acute otitis media with otorrhoea in children between the ages of 2 and 14, and, with the exception of one, there were no recurrences from two to eight months after injection. The discharge ceased on the second or third day and hearing became normal within fourteen days. I gave another course of penicillin to the recurrent case, and the patient has been free from discharge for the last four months. I have also dealt with six cases of otorrhoea due to chronic otitis media, out of which three recurred, the other three having now been free from discharge from eight to thirteen months. One of the recurrent cases had another course of penicillin injections and has now been free from discharge for the last four months.

I give herewith a short history of a case of chronic otitis media:

A man aged 44 developed a right otitis media with otorrhoea 36 years ago. He had been attending hospital ever since and was treated with peroxide ear drops. He was never free from aural discharge for more than two months. His hearing was becoming impaired and he felt dizzy on bending down his head. In November, 1946, I gave him one injection daily of 250,000 units of penicillin calcium in oil-wax suspension for five days. The discharge ceased on the third

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.

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- 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 "prontosil" 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.