the drug at the lower pH. Sulfathiazole is approximately equally active at both pH levels, but the threat of sulfonamide urolithiasis[3] at the lower level should preclude its use in acidic urine. Mandelamine is more effective at pH 5.5 than at 6.5 but at either pH bactericidal concentrations are low enough to permit ready attainment *in vivo* by appropriate dosing.[1] In connection with this heightened activity at the lower pH values, it is to be noted that mandelamine is an acidifying agent, and Carroll and Allen[1] report, "The urine of all patients (200) in the series but 8 became or remained acid on the therapeutic regimen without other medication or restriction of diet or fluid intake."

As shown in Table III, organisms grew in urine which was saturated, at pH 5.5, with sulfathiazole. The degree of resistance which can be developed is necessarily limited by this restricted solubility of the drug, but within this limitation, a 4-fold increase in resistance occurred after as little as 3 to 5 transfers. Resistance to streptomycin developed more rapidly, an increase of 24- to 100-fold being found after 8 to 10 transfers. In contrast to the foregoing, resistance to mandelamine either did not appear, or if it did, it appeared slowly and only to a limited degree; for example, after 9 to 10 transfers there was no change in the susceptibility of 3 organisms, while with the remaining organisms there was only a 3-fold increase in resistance. From the same table, it appears that sulfathiazole-resistant organisms displayed a slightly increased resistance to mandelamine, while the streptomycin-resistant bacteria did not. Further, it appears that mandelamine retained its bactericidal activity against *A. aerogenes H* and *S. aureus* 209, but was only bacteriostatic to the other 4 organisms. These preliminary findings, which suggest that resistance developed against one drug may alter susceptibility to another chemically unrelated drug, are somewhat anomalous, and are being investigated further.

Summary. A comparison of mandelamine, streptomycin and sulfathiazole against 8 stock laboratory strains and 9 strains of organisms recently isolated from urinary tract infections indicates that their activities are not widely different.

In contrast to the results obtained with streptomycin and sulfathiazole, resistance to mandelamine either did not appear, or if it did, it appeared slowly and to a questionable degree in 3 organisms, while in 3 other organisms, resistance did not appear at all.

Organisms rendered resistant to sulfathiazole or streptomycin remain susceptible to mandelamine.

[3] Scudi, J. V., *Am. J. Med. Sciences*, 1946, **211**, 615.

16006 P

Differences During Dicoumarol Therapy in the Quick and Russell Viper Venom Methods for Prothrombin Determination.*

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We recently observed a patient with thrombophlebitis and pulmonary emboli who died in a state of hemorrhagic diathesis during dicoumarol therapy. An average daily dose of 240 mg of dicoumarol administered for 14 days had failed to decrease the prothrombin to the desired therapeutic level as measured by the Russell viper venom modification[1,2] of Quick's method.[3] Subsequently the methods

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[1] Fullerton, H. W., *Lancet*, 1940, **2**, 195.

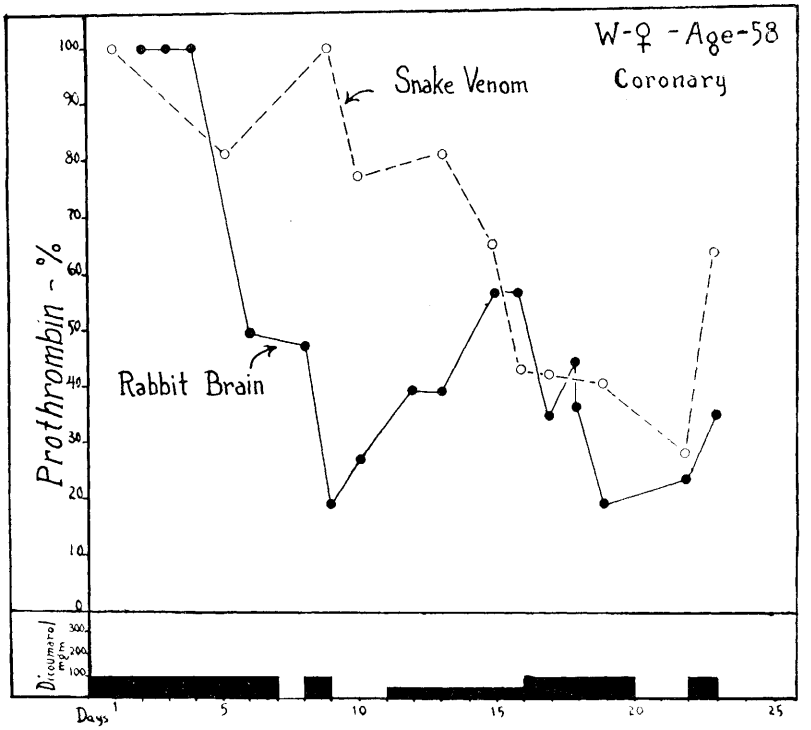

FIG. 1.
Variations in prothrombin during dicoumarol therapy as measured by Quick's method (rabbit brain thromboplastin) and the Russell viper venom modification. Quick's method can be correlated with changes in dicoumarol dosage, the venom method cannot.

of Quick[3] and Page[2] were compared in seven patients receiving dicoumarol therapy.

Striking differences were observed in the quantitative levels of prothrombin as measured by the two methods. Fig. 1 illustrates graphically these variations in a white female who was given dicoumarol orally for coronary occlusion. The therapeutic amounts of dicoumarol, including the initial dosage and changes in the amount of the drug, are closely correlated with the prothrombin levels as determined by the method of Quick, using rabbit brain as the thromboplastin. There is a slow gradual decrease in the prothrombin level as measured by the Russell viper method which cannot be correlated with the Dicoumarol therapy.

Other patients exhibited the same differences. One developed hematuria and it was observed that the prothrombin was less than 5% of normal by the method of Quick and 61% of normal by the Russell viper venom technique. The results of the two methods were not comparable until 4 days later. In all of the patients observed the prothrombin as determined by the method of Quick decreased to the desired therapeutic levels long before there was a decrease by the snake venom method. The levels of prothrombin as determined by the method of Quick could be correlated with the clinical hemorrhagic state of the patients, whereas the amount of prothrombin as determined by the Russell viper venom method resulted in false safe levels. Frequently the patients received too much dicoumarol because of the results of the venom method.

Conclusions. The quantitative values of prothrombin as determined by the method of Quick using rabbit brain thromboplastin can be correlated with dicoumarol therapy and

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[3] Quick, A. J., *J. A. M. A.*, 1938, **110**, 1658.

clinical hemorrhagic tendencies. The levels of prothrombin as determined by the Russell viper venom modification of Quick's method cannot at all times be correlated with the clinical state of the patient and the dicoumarol therapy. The control of dicoumarol therapy by the Russell viper venom method for prothrombin determination is a dangerous procedure. The results may be interpreted as being in a safe therapeutic level of prothrombin when actually the patient may be in a critical potential or actual hemorrhagic condition, this state being determined both by the Quick method and clinical observations.

16007

Electrocardiogram-Electroencephalogram Relations in Cardiac Arrhythmias.

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The initiating relationship of the brain, and in particular of the hypothalamus, to cardiac arrhythmias has been established on both experimental[1-4] and clinical[5-10] grounds. Although a proportion and probably a majority[11,12] of the arrhythmias may find their prime origin in intracardiac derangements, numerous cases of various cardiac arrhythmias are on record[13,14,15] in which the heart is normal. This study contains electroencephalographic data in cases of arrhythmic patients.

The electroencephalograms (EEG) were taken using the hypothalamic lead. Confirmatory electrocardiograms (EKG) were taken in each instance, except one, prior to the EEG. The EEG classification of Gibbs was used in determination of normalcy.† The results are summarized in the table, and tracings in Case 1-1a are reproduced in Fig. 1.

Interpretation. These cases may be divided

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