did not cause stiffness and ulceration of the injection site. As is shown in Fig. 1-C and Table 1, the response of the female rat to chlorpromazine differed significantly from that of the male rat ($S \times T$ in Table 1). Development of tolerance to chlorpromazine in rat was reported by Boyd (2) and Irwin (3). Boyd has used Wahmann drums as index of chlorpromazine effect and showed the development of tolerance to chlorpromazine within four weeks. Irwin has used conditioned avoidance response as index of chlorpromazine effect and recognized the development of tolerance at eighth day. In this experiment, we observed the development of tolerance fifteen days after the beginning of the experiment. At this time, per centage of inhibition of treated rats was statistically different from that of the control. The difference of the periods of the development of chlorpromazine tolerance from that of other investigators should be probably due to difference of strain of rat, experimental method and dose of drug. From the data presented here, no conclusive remark could be drawn on the mechanism of tolerance and the following paper will be reported on the mechanism of tolerance.

REFERENCES

- 1) MATSUKI, K. AND IWAMOTO, T.: THIS JOURNAL **16**, 191 (1966); 2) BOYD, E.M.: *J. Pharmac. exp. Ther.* **128**, 75 (1960); 3) IRWIN, S.: *Archs int. Pharmacodyn. Thé.* **142**, 152 (1963)

CLOSED SEQUENTIAL DESIGN FOR PREFERENCE TEST AT ONE-TAILED 0.05 LEVEL

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Small closed designs are prepared for sequential preference test at the one-tailed 0.05 significance level. The null hypothesis is no preference between treatments, say A and B, existing ($\theta = \theta_0 = 0.5$), and the alternative is A being preferred ($\theta = \theta_1 > 0.5$). Five designs given in Fig. 1 are for the tests with power of 0.95 when the true proportion θ_1 of A-preferences are 0.75, 0.80, 0.85, 0.90 and 0.95, respectively.

For the sake of conformance to Armitage's system (1), the difference Y between the numbers of A-preferences r and non-A-preferences $n-r$ in n times of preference assessments is sequentially plotted against n .

On the basis of the following equation derived from Wald's upper boundary (2)

$$Y_U = \{\log \theta_1 / (1 - \theta_1)\}^{-1} \{2 \log 19 + n \log 0.25 / (1 - \theta_1) \theta_1\}$$

approximate upper boundary points are settled, and then the number ν of different pathways starting at 0 and reaching each boundary point is calculated under the conditions of sequential analysis. The probability of the path reaching a given boundary point is estimated (one by one from the boundary point where $n-r=0$) by the equation

$$\text{Probability } (\theta) = \nu \theta^r (1 - \theta)^{n-r}$$

The maximum required number N of preference assessments is tentatively set up when the cumulative probability of the path reaching the upper boundary points, given $\theta = \theta_1$, is close to 0.95, and at the same time the cumulative probability, given $\theta = \theta_0$, to 0.05. The upper boundary points and N thus obtained are slightly modified in a trial-and-error fashion so as to make the power just larger than 0.95 and the significance level just smaller than 0.05.

FIG. 1. Five types of designs for sequential preference test, $\alpha=0.05$, $1-\beta=0.95$. The sample path starting at 0 moves 1 unit N-E if A is preferred; otherwise (if B-preference is stated), it moves 1 unit S-E. When the sample path crosses the upper boundary the null hypothesis is rejected, and when it hits the lower boundary the null hypothesis is not rejected. Non-preference is to be neglected in plotting.

Finally the lower boundary points are settled on a 45° line starting at the point 2 units lower than the upper boundary point at N .

The designs given in this paper may be further modified to obtain improved designs or skew designs (1).

REFERENCES

- 1) ARMITAGE, P.: *Sequential Medical Trials*, Blackwell Sc. Pubs., Oxford (1960); 2) WALD, A.: *Sequential Analysis*, John Wiley & Sons, Inc., New York (1947)

Added in Proof: Dr. Armitage and Mr. McPherson have kindly calculated the exact α and β values from their computer program. The values are :

θ_1	.75	.80	.85	.90	.95
α	.0452	.0432	.0471	.0477	.0483
$1-\beta$	.9536	.9550	.9598	.9507	.9845

FAILURE OF KININ FORMATION BY GLASS POWDER IN RAT PLASMA AFTER INJECTION OF BROMELAIN

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It was reported from this laboratory that pretreatment of rats with stem bromelain (BM) prevents lung edema produced by adrenaline infusion, but not with papain (PAP), although both enzymes are similar thiol-