The so-called "step-wise" analysis method has been used widely in regression analysis.[15] Although discriminant analysis uses the general multivariate linear model[16] and is similar to regression analysis, methods of selecting variables are not extensively discussed in the literature. Currently, Biomedical Computer Programs (BMD)[17] and the Statistical Package for Social Sciences[18] are programs that include step-wise discriminant analysis routines. Recently, McCabe[19] proposed an algorithm for all possible subsets of any given size and compared results with the BMD procedure. Although this new algorithm seems to be a great improvement, it requires excessive computer storage and time and appears impractical for studies with more than 20 variables. The present study used a step-wise discriminant analysis program named BMD07M, which is part of the BMD package.[17]

After a set of variables is determined that provides satisfactory discrimination for patients with known group membership, a set of classification functions can be derived that will permit the classification of new patients with unknown outcome. For this purpose the so-called Bayesian theorem or rule may be applied. Mathematical aspects of Bayes' rule may be found in most statistics books,[20] and clinical applications of Bayes' rule have also been discussed.[21]

In its simplest form Bayes' rule may be written as follows:

$$P(H_i|z) = \pi_i P(z|H_i) / \sum_{i=1}^{k} \pi_i$$

$$P(z|H_i) \quad i = 1, 2, \ldots k$$

where $\{\pi_i\}$ are the so-called prior probabilities, $P(z|H_i)$ are the conditional probabilities of obtaining discriminant scores of z or greater if the subject belongs to the ith group, and $P(H_i|z)$ are the so-called posterior probabilities — the probabilities of belonging to each group when the information given by z is taken into account. An example application of this formula is given in the main part of this paper. ■

Long-term therapy of essential tremor with propranolol

T.J. MURRAY, MD

In a double-blind crossover study 12 patients with essential tremor were treated with propranolol and a placebo; 8 improved with propranolol and 3 with the placebo; the degree of improvement with propranolol was greater. In a similar study with diazepam 5 of 12 improved with diazepam and 4 of 12 with the placebo; the degree of improvement was less than that achieved with propranolol.

Response in 21 patients to treatment with propranolol for 2 to 4 years was excellent in 4, good in 4 and fair in 10; the condition of 1 was unchanged and that of 2, worse. Excellent response was maintained for as long as 4 years, but response tended to deteriorate with time if initially it was less than excellent. Response decreased with increasing age. No patient 60 years of age or older had an excellent response, and the four with an excellent response were under age 55, three being under age 35; all four had had their tremor less than 12 years.

Patients with essential tremor should be given a 3-month trial of propranolol at 120 mg/d; if no significant response is seen the dose should be decreased, then the drug discontinued.

Dans une étude à double insu avec chassé-croisé 12 patients souffrant de tremblement essentiel ont reçu du propranolol ou un placebo; 8 se sont améliorés sous propranolol et 3 sous placebo; on a constaté un taux d'amélioration supérieur avec le propranolol. Dans une étude identique, 5 patients sur 12 se sont améliorés avec le diazépam et 4 sur 12 avec le placebo; l'amélioration a été moins marquée qu'avec le propranolol.

Chez 21 patients ayant reçu du propranolol pour des périodes de 2 à 4 ans la réponse a été excellente dans 4, bonne dans 4 et moyenne dans 10; l'état d'un patient est demeuré inchangé, alors qu'il s'est aggravé chez 2 d'entre-eux. Une excellente réponse a pu être maintenue jusqu'à 4 ans, mais une réponse initiale moins qu'excellente avait tendance à se détériorer avec le temps. La réponse a diminué en fonction de l'âge. Aucun patient âgé de 60 ans ou plus n'a eu une excellente réponse, alors que les quatre patients bénéficiant d'une excellente réponse étaient âgés de moins de 55 ans, dont trois de moins de 35 ans; tous quatre souffraient de tremblement depuis moins de 12 ans.

Les patients atteints de tremblement essentiel devraient recevoir un traitement d'essai de 3 mois au propranolol à la dose de 120 mg par jour; si aucune réponse significative ne peut être observée, la dose devrait être diminuée, puis le traitement interrompu.

In 1971 Winkler and Young[1,2] observed that the β-adrenergic blocking agent propranolol was beneficial to patients with essential tremor. In 1972 I reported the findings of a preliminary study of 12 patients treated with propranolol for essential tremor; excellent results were obtained in 6 and lesser improvement in 6.[3] There are now several further reports on propranolol therapy for essential tremor,[1-14] most confirming its value. However, in general, these are anecdotal or represent short-term, often uncontrolled studies. In this paper I report the results of a double-blind study with propranolol, a separate double-blind study using diazepam for comparison, and a long-term follow-up of 21 patients treated with propranolol for 2 to 4 years.

Methods

From 1971 to 1975, 41 patients with essential tremor were assessed for possible inclusion in a study of long-term propranolol therapy. Three were eliminated because of asthma or borderline cardiac output, three because they did not wish to take a medication for a long period and six because of serious concomitant disease. Five patients were given therapy but not studied further because of distance or noncooperation. The remaining 24 patients entered short-term double-blind studies and 21 were followed up while taking propranolol for 2 to 4 years.

Initially a double-blind crossover study was completed for 12 patients, each receiving 120 mg of propranolol daily for 6 weeks and a placebo for 6 weeks. Assessments included examination and evaluation of the tremor by a five-grade system, the patient's subjective evaluation of change, and study of the patient's handwriting and ability to draw an Archimedes spiral. The effect on the tremor when the patient was angry, under stress or in other circumstances of heightened emotion was also evaluated. However, only the evaluation of the tremor proved to be a true measure of response to therapy; hence the complex scoring system was abandoned and only the five-grade evaluation of tremor retained.

Because the value of propranolol could be attributed to its effect on anx-

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iety, a similar double-blind crossover study was conducted in the other 12 patients with a placebo and diazepam to assess the merit of an antianxiety agent.

Results

The response to propranolol was significantly better ($X^2 = 7.05$; $P < 0.005$) than that to placebo (Table I). In three cases the tremor almost disappeared. When asked to select the drug that gave them the best results, nine patients chose propranolol, two placebo and one neither. The two who selected placebo discontinued it at 6 and 9 weeks, respectively, because they thought it was no longer of benefit; the observed placebo effect was short-lived. The patients who selected propranolol continued taking it long-term.

In the diazepam and placebo study there were no excellent responses in either group and the overall response was much poorer than in the propranolol and placebo study (Table II). Although diazepam was not shown to be significantly more effective than placebo, at the end of the trial six patients selected diazepam, two placebo and four neither. Some said they felt less tense while taking diazepam.

The results of 2 to 4 years of treatment with propranolol in 21 patients are shown in Table III. Those with excellent response early in the study, two of whom had been taking the medication for over 4 years, retained that level of response. However, those with a response that was initially less than excellent tended to have poorer responses with time, which suggests a slow increase in the tremor despite propranolol therapy. Larger doses of propranolol did not improve the response. However, three patients with only fair initial responses thought their tremor was appreciably worse when they stopped taking the medication and requested reinstitution of therapy.

Table I—Responses to propranolol and placebo of 12 patients with essential tremor

	No. of patients	
Response*	Propranolol	Placebo
Excellent	3	0
Good	4	1
Fair	1	2
None	4	9
Worse	0	0
% improved	67†	25†

*Excellent: tremor absent or present only occasionally; good: tremor present but greatly reduced; fair: tremor present but slightly reduced.
†This difference is significant at $P < 0.005$; $X^2 = 7.05$ with 3 degrees of freedom.

Factors governing response

Response decreased with increasing age, as Table IV shows. Of the patients 60 years of age or older (71%) none had an excellent result (Table III). The four with excellent response were under age 35 and had had the tremor less than 12 years.

Response also decreased with longer duration of the tremor. All patients with an excellent result had had the tremor less than 15 years, the average being 9.7 years, whereas for the patients with no change the average duration was 20.5 years. Patients whose condition worsened during long-term follow-up had had their tremor an average of 25 years.

Although many factors were assessed to evaluate response to propranolol, those that were relevant — for example, evidence of mild extrapyramidal features — related to the patient's age. The patient's sex, response to other medication, positive family history, various aggravating factors, response to alcohol, or number of siblings did not appear to be governing factors.

Table II—Responses to diazepam and placebo of 12 patients with essential tremor

	No. of patients	
Response	Diazepam	Placebo
Excellent	0	0
Good	2	2
Fair	3	2
None	7	8
Worse	0	0
% improved	42	33

Table III—Response to long-term treatment with propranolol of 21 patients with essential tremor

		Age (yr)	
Response	All patients	<60	⩾60
Excellent	4	4	0
Good	4	1	3
Fair	10	1	9
None	1	0	1
Worse	2	0	2

Table IV—Average age of patients in response groups

Response	Average age (yr)
Excellent	34.2
Good	63.0
Fair	65.0
None	70.5
Worse	72.0

Almost all patients found their tremor aggravated by stress or anxiety, especially if they thought they were being watched or were around strangers. In none did caffeine aggravate the tremor. Of the patients who drank alcohol, 75% obtained relief from their tremor with small amounts, but 43% of the overall group were teetotallers.

Two other factors correlated with a negative therapeutic result: severely impaired handwriting and an action component to the tremor. In addition, patients who appeared to have a mixed parkinsonian and essential tremor, but had no other symptoms of Parkinson's disease, responded poorly to propranolol.

Dana[15,16] once commented that patients with essential tremor were characterized by longevity and fecundity. We could confirm neither feature in our patients but the average number of siblings was 4.6, which is greater than in the normal population. Fifty percent of patients had a family history of essential tremor, an average of 3.4 family members being affected.

Discussion

Patients with essential tremor consult physicians because their problem is distressing and embarrassing.[17] Before Winkler and Young[1,2] observed that propranolol benefited these patients it was generally accepted that there was no effective treatment for the condition. Although some patients do not respond to propranolol as well as was hoped, many neurologists have achieved good results with it, and a number of reports advocate its use.[1-12]

Dupont, Hansen and Dalby,[11] using simple clinical tests for evaluating changes in tremor, reported that propranolol gave better results than placebo, and that the placebo response was short-lived. In a long-term study they found that, while taking 120 mg of propranolol daily, 5 patients were completely free of tremor, in 15 the tremor was reduced by various degrees and in 10 the tremor was unchanged. The effect was considerably better in younger patients with a shorter duration of tremor. They found that propranolol was the most effective drug known for treating benign essential tremor.

Sweet and colleagues[12] concluded from a double-blind crossover study of nine patients that propranolol does not benefit all patients with essential tremor but that those "with clearcut essential tremor unresponsive to sedatives should try propranolol".

In contrast to these positive reports, two letters to the editor of *The Lancet*

reported negative findings. After treating a number of patients Balla[13] noted equal improvement in both the propranolol and placebo groups. Foster, Longley and Stewart-Wynne[14] found that essential tremor was not significantly decreased in 14 patients completing their trials, but 4 of these thought they had improved.

Claims for propranolol's effectiveness in treating various conditions are steadily increasing in number. Drew, Moon and Buchanan[18] commented that propranolol may provide a significant advance in treating alcoholic patients. Six of 50 patients who had been embarrassed by chronic tremor all of their adult lives showed striking improvement when their alcoholism was treated with propranolol. Most thought their tremor was an important reason for their initial and continuing abuse of alcohol. The tremor occurring during alcohol withdrawal was also excellently and quickly controlled with propranolol. Propranolol has also been found useful in treating angina,[19] thyrotoxicosis,[20,21] acute anxiety,[22] migraine,[23] schizophrenic symptoms[24] and Parkinson's disease.[25] It has also been shown to reduce the tremor induced by lithium.[26]

Whether the effect of propranolol on essential tremor is central or peripheral in the nervous system is uncertain. Anctil, Hugues and Marche[27] have shown that intravenous administration of propranolol reduces the speed of conduction in the popliteal and sciatic nerves of healthy persons and can suppress muscular activity of subjects with chronic idiopathic tetany. This suggests a peripheral action. On the other hand, Growdon, Shahani and Young[28] found that oral administration of alcohol decreased essential tremor, whereas intra-arterial administration did not. This suggests a central mechanism for the effect of alcohol on essential tremor. Kissell, Tridon and André[25] noted that practolol, a β-adrenergic blocking agent that does not pass the blood–brain barrier, does not reduce tremor in parkinsonism; this suggests that propranolol acts centrally by stabilizing neuronal membranes rather than by its β-adrenergic properties. Marshall[29] has mustered evidence based on frequency studies to suggest that essential tremor may be accentuated physiologic tremor.

My experience in using propranolol to treat other neurologic disorders, particularly movement disorders, has been consistently disappointing. Results in the treatment of spasmodic torticollis, tardive dyskinesia, red nucleus tremor and benign essential myoclonus have been completely negative. In different cases I have also used propranolol in the treatment of parkinsonian tremor with and without levodopa and the dopa decarboxylase inhibitor RO-44-602, but the results have been poor. I have treated 2 patients with acute hyperventilation anxiety with good results, 18 with migraine with variable but often striking improvement, and 2 with severe tremor in multiple sclerosis with surprisingly good results.

In the present study no major side effects from the use of propranolol were observed, although some patients complained of tiredness and a few of increased dreaming. A recent report stated that a small number of patients taking propranolol for angina will have an increase in their angina and perhaps even a myocardial infarction if the drug is suddenly discontinued.[30] I know of no report of this occurring in patients taking propranolol for essential tremor, but have adopted the policy of discontinuing the drug slowly when withdrawal becomes necessary.

Ashenhurst[31] concluded from analysis of 34 patients that essential tremor is a monosymptomatic condition and that the tremor is both postural and induced by action. Although many associations of unusual diseases with essential tremor are merely chance observations, essential tremor may be the initial manifestation of a number of abnormalities of the central nervous system, of both a sporadic and a familial nature; a number of my patients have begun to show mild but definite extrapyramidal changes typical of Parkinson's disease many years after a typical course of essential tremor. My long-term observations suggest that there is a spectrum of manifestations due to specific or diffuse neuronal abnormalities in the cerebellar–basal ganglia system, with an overlap among benign essential tremor, Parkinson's disease, the tremor of degenerative cortical disease and the tremor of "senility". The differentiation of essential tremor and parkinsonism may be difficult in the elderly with extrapyramidal features, for many consider extrapyramidal features to be part of "normal" ageing, and essential tremor is common in this age group.

Conclusions

In the long-term treatment of essential tremor with propranolol a small proportion of patients will show continuing excellent amelioration of their tremor. The remainder will respond well initially but their condition will deteriorate slowly. Increasing the dose of propranolol or adding other medications is of no value.

Factors that seem to forecast a good response to propranolol are younger age, particularly less than 55 years, duration of tremor less than 15 years, normal handwriting, and the absence of both extrapyramidal features and an action component to the tremor.

Patients with essential tremor should be given a 3-month trial of propranolol, 120 mg/d. If no definite response is seen there is no value in increasing the dose or continuing the drug. However, a small number of patients will respond extremely well to this therapy and many others will be improved by it.

References

1. WINKLER GF, YOUNG RR: The control of essential tremor by propranolol. *Trans Am Neurol Assoc* 96: 66, 1971
2. Idem: Efficacy of chronic propranolol therapy in action tremors of the familial, senile or essential varieties. *N Engl J Med* 290: 984, 1974
3. MURRAY TJ: Treatment of essential tremor with propranolol. *Can Med Assoc J* 107: 984, 1972
4. SEVITT I: The effect of adrenergic beta-receptor blocking drugs on tremor. *Practitioner* 207: 677, 1971
5. PAKKENBERG H: Propranolol in essential tremor. *Lancet* 1: 633, 1972
6. GILLIGAN BS, VEALE JL, WODAK J: Propranolol in the treatment of tremor. *Med J Aust* 1: 320, 1972
7. GILLIGAN B: Propranolol in essential tremor. *Lancet* 2: 980, 1972
8. SCOPA J, LONGLEY BP, FOSTER JB: Beta-adrenergic blockers in benign essential tremor. *Curr Ther Res* 15: 48, 1973
9. MORGAN MH, HEWER RL, COOPER R: Effect of beta adrenergic blocking agent propranolol on essential tremor. *J Neurol Neurosurg Psychiatry* 36: 618, 1973
10. BARBEAU A: Traitement du tremblement essentiel familial par le propranolol. *Union Med Can* 102: 899, 1973
11. DUPONT E, HANSEN HJ, DALBY MA: Treatment of benign essential tremor with propranolol. *Acta Neurol Scand* 49: 75, 1973
12. SWEET RD, BLUMBERG J, LEE JE, et al: Propranolol treatment of essential tremor. *Neurology (Minneap)* 24: 64, 1974
13. BALLA JI: Treatment of essential tremor with propranolol. *Lancet* 1: 205, 1973
14. FOSTER JB, LONGLEY BP, STEWART-WYNNE EG: Propranolol in essential tremor. Ibid, p 1455
15. DANA CL: Hereditary tremor, a hitherto undescribed form of motor neurosis. *Am J Med Sci* 94: 386, 1887
16. Idem: The clinical characters and diagnostic significance of tremor. *Med News* 61: 673, 1892
17. CRITCHLEY M: Observations on essential (heredofamilial) tremor. *Brain* 72: 113, 1949
18. DREW LRH, MOON JR, BUCHANAN FH: Inderal (propranolol) in the treatment of alcoholism. *Med J Aust* 2: 282, 1973
19. HEBB AR, GODWIN TF, GUNTON RW: A new beta adrenergic blocking agent, propranolol, in the treatment of angina pectoris. *Can Med Assoc J* 98: 246, 1968
20. GIBBERD MG, STAFFURTH JS: Oxprenolol in thyrotoxicosis. *Lancet* 1: 205, 1973
21. SHANKS RG, HADDEN DR, LOWE DC, et al: Controlled trial of propranolol in thyrotoxicosis. *Lancet* 1: 993, 1969
22. TURNER P, BONN JA: D-propranolol and anxiety. *Lancet* 1: 1355, 1971
23. WEBER RB, REINMUTH OM: The treatment of migraine with propranolol. *Neurology (Minneap)* 22: 366, 1972
24. YORKSTON NJ, ZAKI SA, MALIK MK, et al: Propranolol in the control of schizophrenic symptoms. *Br Med J* 4: 633, 1974
25. KISSEL P, TRIDON P, ANDRÉ JM: Levodopa–propranolol therapy in parkinsonian tremor (C). *Lancet* 1: 403, 1974
26. KIRK L, BAASTRUP PC, SCHOU M: Propranolol treatment of lithium-induced tremor. *Lancet* 2: 1086, 1973
27. ANCTIL R, HUGUES FC, MARCHE J: Action du propranolol sur la conduction nerveuse chez l'homme. Premiers résultats dans la tétanie chronique idiopathique de l'adulte (spasmophilie). *Therapie* 25: 579, 1970
28. GROWDON JH, SHAHANI BT, YOUNG RR: The effect of alcohol on essential tremor. *Neurology (Minneap)* 25: 259, 1975
29. MARSHALL J: Observations on essential tremor. *J Neurol Neurosurg Psychiatry* 25: 122, 1962
30. ALDERMAN EL, COLTART DJ, WETTACH GE, et al: Coronary artery syndromes after sudden propranolol withdrawal. *Ann Intern Med* 81: 625, 1974
31. ASHENHURST EM: The nature of essential tremor. *Can Med Assoc J* 109: 876, 1973