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Autonomic and Psychic Effects of Yohimbine Hydrochloride

By

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With 4 Figures in the Text

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During the last 20 years various attempts have been made at obtaining reliable tests of autonomic reactivity in mentally ill individuals. Mostly epinephrine and methacholine have been used to induce blood pressure changes, the degree and patterns of which have been claimed to differentiate diagnostic and prognostic categories (MYERSON et al.; LINDEMANN and FINESINGER; FUNKENSTEIN et al. 1950). However, FUNKENSTEIN found the epinephrine test in itself to be without predictive value for the outcome of treatment (FUNKENSTEIN et al. 1952). Other authors have more and more tended to conclude that the methacholine test is only vaguely associated with prognostic factors (SLOANE et al. and LUNDE et al.), and lately most authors have completely failed to find any prognostic value in the test procedures (HOFFER and CALLBECK 1959a; SATTERFIELD; OZTURK et al.; BRAUN and RETTEK; BRILL et al.).

Atropine is another drug which has been used to differentiate groups of mentally ill patients. HOFFER (1954, 1959b) found that schizophrenic cases differed from normal individuals in that they showed a lesser increase or even a decrease in blood pressure in response to this drug. He did not, however, consider the atropine test more accurate than the ordinary diagnostic procedure and thus not of any practical use. It has also been reported that schizophrenics usually give more variable blood pressure reactions to atropine than do normal subjects (DOUGLAS and HOCH).

Barbiturate sedation has been introduced by SHAGASS (1954, 1956) as a tool for determination of the degree of tension and anxiety and for differentation between neurotic and psychotic types of depression. Other authors, however, have found this method of low objectivity (THORPE and BARKER; BRADLEY and JEAVONS) and recently ACKNER (1959) — in spite of all efforts to make the procedure objective and reliable — did not find any significant correlation between test results and anxiety or tension.

In view of the undoubted association between mental disorder and autonomic reactivity a search was made for drugs with adrenergic

blocking properties. Yohimbine hydrochloride (Fig. 1) among others was tried. Yohimbine in fairly high doses in animals exerts adrenolytic effects, and in still higher doses produces sympathetic nerve blockade
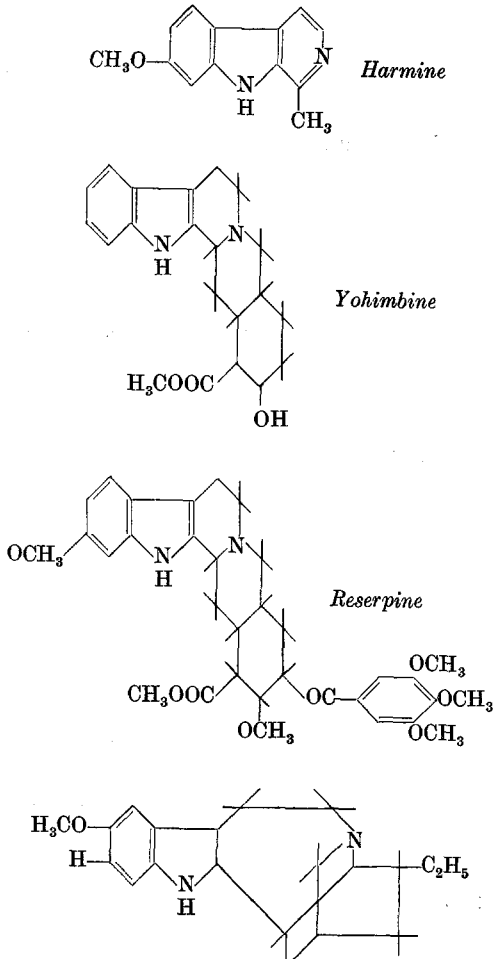

Fig. 1

(RAYMOND-HAMET; BARRY; YONKMAN et al.; BOVET and BOVET-NITTI; NICKERSON). The central nervous system actions are reported to be less prominent than those of the ergot alkaloids and benzodioxanes. No clinical experiences with yohimbine have been reported, and GOOD-MAN and GILMAN state that the drug has no proven therapeutic uses. We found this drug to have interesting autonomic and psychic effects which were correlated with the emotional reactivity of the subjects used

(HOLMBERG and GERSHON); and decided that yohimbine warranted more detailed studies to evaluate further its usefulness as a clinical test drug and to investigate its mode of action.

Materials and Methods

A total of 60 cases was studied. Ten cases were used for experiments on modification of epinephrine reaction, seven of which also were used in studies of the preventative effects of sedatives. Three separate groups, of 15 schizophrenic patients, 9 normal volunteers, and 20 mental hospital patients with mixed diagnoses, were used in studies of the relation of yohimbine effects to emotional reactivity. Six further patients were given repeated doses of yohimbine for a study of its psychic effects.

It is considered essential for effective rating that a wide spectrum of patient material be studied, and that the observations be carried out in a stable ward environment for at least three weeks.

For the injection of autonomic drugs we adopted throughout the intravenous route at a constant dose rate. Before each experiment, a heparinized intravenous cannula was inserted and fixed on the arm. Through a rubber membrane on the cannula, injection could later be made as many times as needed without any pain or delay for puncture.

The dose of yohimbine was 0.5 mg/kg, given at an even rate over a period of five minutes. Immediately before the injection a five minute baseline recording was done, and after the injection the effects were observed for at least 15 minutes. During this whole procedure the EKG was recorded continuously and blood pressure taken by auscultation every 30 seconds. In some cases respiration and skin temperature were also recorded and the observation time extended over one hour (see section on direct autonomic effects). The autonomic effects of preparatory procedures (needle insertion and saline injection) were also recorded in connection with the studies of the relationship between yohimbine effects and emotional reactivity.

Emotional reactivity was rated individually by seven skilled raters, using a scale with eight points.

Table 1. *Scale for rating of emotional reactivity*

0	Very little sign of any reactions (more or less stuporous)
1	Definitely (pathologically) sub-reactive
2	Somewhat sub-reactive (the lowest a healthy person could possibly go — many mentally ill people should also fall into this group)
3	Normally reactive (without obvious signs of nervousness)
4	Somewhat over-reactive (a little nervous)
5	Rather over-reactive (quite nervous but not to a definitely pathological degree)
6	Definitely over-reactive (shows abnormal degree of fear and anxiety)
7	Strongly over-reactive (which means that the patient is among the most tense and anxious cases that can be managed in experiments)

The raters were instructed to note especially the reactions of anxiety or fear seen in the subjects during a two-month period of observation. Also the subjects were rank-ordered in the same respect, and the mean ranking list was used for a rank-order correlation (KENDALL) with the autonomic effects of yohimbine. The individual raters were found to be in good agreement, as KENDALL's coefficient of concordance was .827 ($P < .001$).

Results

Direct autonomic effects. The initial response to the injection of yohimbine was facial flushing and an increase in heart rate. Following this, perspiration, salivation, lachrymation, and pupillary dilation were observed, concomitant with a rise in blood pressure. In the more markedly affected cases, nausea and sometimes urgency of micturition and defecation occurred. Erection was observed in 10—20% of the cases, apparently unrelated to other signs and symptoms.

In all our subjects the maximum heart rate increase ranged from 4 to 48 beats per minute. The peak generally was reached during or immediately after the period of yohimbine injection, while return to baseline varied from 3 to over 55 minutes. Those cases that exhibited a less marked rise in heart rate usually showed a secondary drop below baseline.

Systolic blood pressure rose by 2—93 mm. Hg., and this occurred more slowly than the heart rate response. The maximum increase occurred 5—20 minutes after the injection, and the increase frequently lasted longer than 55 minutes (Fig. 2). Diastolic pressure generally showed a more moderate rise.
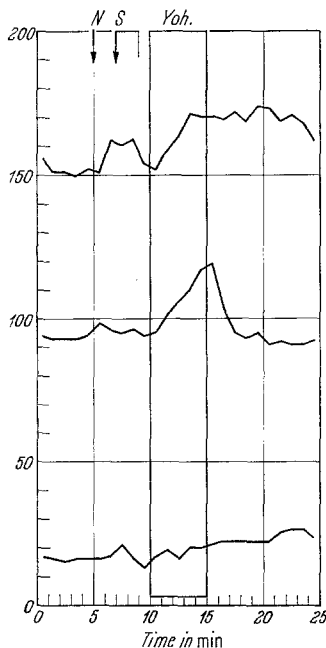

Fig. 2. The effect in one case of preparatory procedures (N needle insertion, S saline injection) and infusion of yohimbine 0.5 mg/kg (Yoh.) on systolic blood pressure mm Hg (upper curve), heart rate beats/min (middle curve) and respiratory rate/min. (lower curve)

The respiratory rate and volume usually increased a little. Hand temperature generally fell, in most cases followed by a secondary rise. Other autonomic signs essentially paralleled the degree of heart rate change.

Modification of epinephrine reaction. In a group of 10 cases, consisting of five schizophrenics, two sociopaths, two alcoholics and one syphilitic chronic brain syndrome, epinephrine tests were performed

Table 2

	Epinephrine alone			Epinephrine after yohimbine		
	Baseline	Epi-nephrine	Difference	Baseline	Epi-nephrine	Difference
Heart rate Beats per minute	87.4	91.1	+ 3.7	84.3	108.0	+23.7
Blood pressure Systolic mm Hg	132.2	162.9	+30.7	146.2	163.5	+17.3

15 minutes before and 15 minutes after yohimbine administration. The epinephrine dose was 0.20 γ/kg/min given intravenously over a period of three minutes.

As is seen from Table 2 epinephrine produced a significantly greater increase in heart rate after yohimbine than it did alone, an average
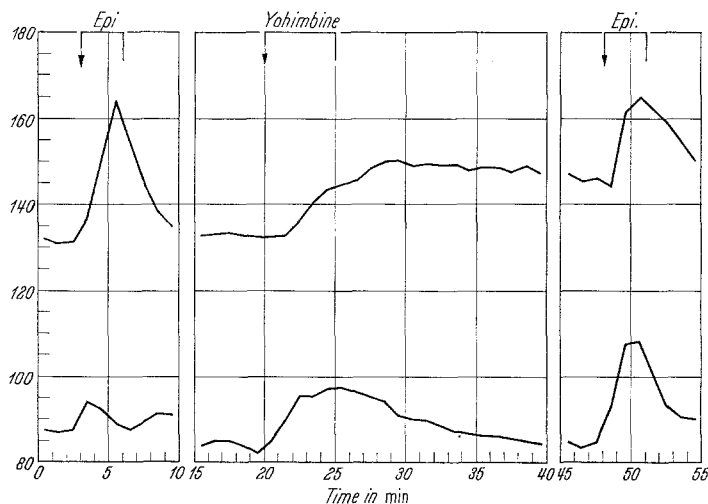

Fig. 3. The effect on systolic blood pressure mm Hg (upper curve) and heart rate beats/min. (lower curve) of epinephrine infusion (Epi), before and after yohimbine infusion. For dosage, see text

20 beats/minute more (range +6 to +38). This difference was significant at the 0.1 % level. While in two cases the heart rate had decreased before, it now increased in all ten cases from epinephrine.

The blood pressure after yohimbine was elevated to a higher level than before. The increase obtained with epinephrine now was less marked, an average 13.4 mm Hg less (range −51 to +6). This difference was significant at the 5% level only. The actual blood pressure obtained with epinephrine was generally at least as high as before, except in two cases where the increase before yohimbine was unusually high (over 200 mm Hg). In these cases the blood pressure obtained after yohimbine was within a more normal range. See Fig. 3.

A further observation was that certain of the effects usually obtained with yohimbine, such as tremor, flushing and restlessness, became more marked when epinephrine was superimposed.

Effect of sedatives on the autonomic changes. Seven of the 10 subjects of the above group were given amobarbital sodium 6.25 mg/kg intravenously prior to the administration of yohimbine. The sodium amytal put all, except one, into a light sleep which lasted throughout the whole test period. Following the amytal, blood pressure was lowered and heart rate was somewhat accelerated. Yohimbine given at this point did not markedly change heart rate; there was a mean decrease of 1.6 beats/min. as compared to an increase of 11.8 beats/min. when no sodium amytal had been given (difference significant at the 1% level). Blood pressure increased by 9.9 mm Hg from yohimbine as compared to 16.6 mm Hg when no sodium amytal had been given. Thus the sodium amytal abolished the heart rate increase but only reduced the blood pressure increase by 40% ($P < .05$). See Fig. 4. In no case so treated did the yohimbine produce any other visible autonomic changes such as perspiration, flushing, or change in respiration.
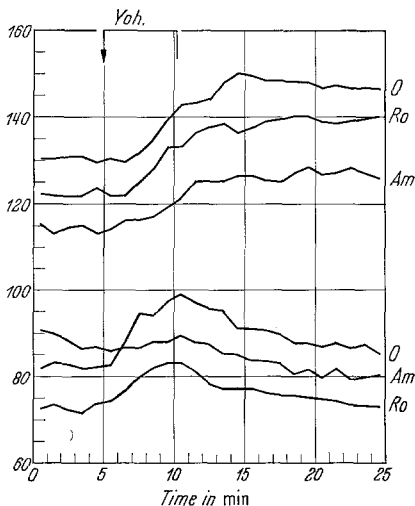

Fig. 4. The effect of yohimbine infusion on systolic blood pressure mm Hg (the three upper curves) and heart rate beats/min. (lower curves) without premedication (0), after i. v. injection of amobarbital sodium *(Am)* and after Ro 5—0690 *(Ro)*. For dosage see text

Ro 5—0690 (7-chloro-2-methylamine-5-phenyl-3H-1,4-benzodiazepine 4-oxide hydrochloride[1]) 1.5 mg./kg. given by slow intravenous injection to the same seven individuals 15—20 minutes before the yohimbine test put only one of the subjects to sleep and made the others slightly drowsy. This level of depression was considerably less than seen with amobarbital; they could rationally respond to questions but with definite slurring of speech. Both heart rate and blood pressure were somewhat lowered by this drug. Yohimbine gave a heart rate rise of 6.7 beats/min. and a blood pressure rise of 15.8 mm Hg, which means a reduction by 43% ($P < .20$) and 5% (not statistically significant) respectively, compared with the response to yohimbine alone. The other visible autonomic changes were reduced but not to the same extent as with amobarbital.

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[1] This preparation (Librium) was provided by Hoffmann La Roche Co.

Effect of medication with imipramine. Seven subjects (four schizo-phrenics, one alcoholic and two sociopaths) were studied to determine the effects of imipramine medication on the response to yohimbine. The imipramine was started after the first yohimbine test. The subjects were given a daily oral dosage of approximately 3 mg/kg body weight divided in three doses daily for three weeks, after which the second yohimbine test was carried out.

The average heart rate rise produced by yohimbine before imi-pramine was from 72 to 89 (difference $+17$) beats/min. The baseline heart rate was increased while on imipramine medication to an average of 96 beats/min, and there was a further rise after yohimbine injection to 125 beats/min. (difference $+29$).

The blood pressure increased from an average of 116 to 130 (difference $+14$) mm Hg from yohimbine alone, and after imipramine medication the increase was from 119 to 167 (difference $+48$) mm Hg. Concomitant with this very marked and statistically significant increase in the yohim-bine effects brought about by the imipramine, there was also a poten-tiation of the other autonomic effects. There was a significant increase in the degree of flushing, perspiration, tremor, and nausea above that induced by yohimbine alone.

Relation of autonomic changes to emotional reactivity. By obser-vation of the patients during the yohimbine test it became evident that the overall degree of effect of the drug had a connection with the pre-existing emotional reactivity of the individual. A statistical correlation was shown to exist between the heart rate change obtained with yohim-bine and the rated level of emotional reactivity. On the other hand, no such correlation existed between the degree of blood pressure change and emotional reactivity.

In the first group, consisting of 15 schizophrenic patients, the cor-relation between heart rate increase from yohimbine and emotional reactivity was .739 ($P<.01$). In the second group, consisting of nine normal volunteers, findings were very similar, and the correlation was .925 ($P<.01$). In the third group, consisting of 20 mental hospital patients with varying diagnoses, again a correlation could be shown to exist, $r_s = .605$ ($P<.01$). It could thus be safely stated that the heart rate increase obtained from yohimbine injection had a definite relation-ship to the basic emotional reactivity.

In none of these three populations did the degree of blood pressure increase have any significant correlation to emotional reactivity, $r_s = -.293$, .160, and .086 respectively. In the first group there was a correlation between the duration of the blood pressure increase and the emotional reactivity, $r_s = -.526$ ($P<.05$). No such correlation existed in the latter two populations.

In the first as well as in the second group the baseline heart rate (as measured in the experimental situation) before the test correlated equally well with emotional reactivity, $r_s = .732$ and 892 respectively ($P < .01$). In the third group the correlation was insignificant (.018) probably because these were patients that had become familiar with the various laboratory procedures. Only in the first sample did a significant correlation exist between baseline blood pressure and emotional reactivity, $r_s = .746$ ($P < .01$), while in the latter two the correlations were as low as .075 and $-.194$.

The effect on heart rate of preparatory procedures (insertion of an intravenous needle, injection of normal saline) correlated significantly with emotional reactivity in the first sample, $r_s = .610$ ($P < .05$), while the correlations in the second ($r_s = .579$) and in the third (.377) were not significant. There was a significant correlation between the rise in heart rate from the preparatory procedures and that from yohimbine injection, $r_s = .753$ ($P < .01$) in the first group, and in the second $r_s = .667$ ($P < .05$). In the third the correlation (.338) was not significant. Only in this last group was there a very significant correlation between emotional reactivity and the blood pressure effect of the preparatory procedures, $r_s = .697$ ($P < .001$). In the first two groups the correlations were not significant.

The relationship found between emotional reactivity and the effect of the drug on heart rate was evidently fairly independent of diagnostic categories. It existed in the first schizophrenic group as well as in the normal volunteers. It also existed in the third group, consisting of both psychotic and non-psychotic mental hospital patients. When this latter group is broken up into one part consisting of 12 schizophrenic patients and one part consisting of eight non-schizophrenic patients (psychopathic and alcoholic cases and one case of syphilitic brain damage), the correlation within each of the parts is somewhat higher than for the total group (.729 in the schizophrenic group and .792 in the non-schizophrenic group). When the heart rate increase from yohimbine in the 12 schizophrenics is compared to the increase in the eight non-schizophrenics, there is no significant difference. The range of heart rate change (mean over a 5 minute period) in the schizophrenic group was -1.0 to $+22.4$ (mean $+10.2$), and in the non-schizophrenic group $-.2$ to $+27.2$ (mean $+10.0$) beats/min. This lack of difference is apparently due to the fact that the schizophrenic patients showed all degrees of emotional reactivity, from strongly over-reactive to very unreactive states (score .7—6.1, mean 2.40), while the non-schizophrenic cases were scattered in a similar way, only within a somewhat narrower range (score 1.3—4.8, mean 3.25). The latter material of 20 cases was checked for possible correlations between drug effect on the one hand

and age, time of stay in the hospital, and body weight on the other hand. None of these correlations was significant even on the 10% level.

To date only one depressive has had the yohimbine test, a 48 year old man who has had two manic episodes on previous occasions and this time was admitted with endogenous depression. He was almost mute, showed signs of great fear and anxiety, and had classical delusions of a melancholic type. This case showed the most marked heart rate and blood pressure changes that we have seen. The maximum heart rate was 136 beats/min. and maximum blood pressure 208 mm Hg. It took more than one hour before these changes had subsided. Also salivation, flushing, sweating, and lachrymation were of severe degree. Erection was also observed.

Psychic effects. Concomitant with the autonomic response to yohimbine, psychic changes were also observed, simulating an anxiety state. The subjects displayed a tense and anxious facial expression. They became restless, irritable, tremulous, and feelings of impatience and unrest were often experienced. In the few cases where this state was very marked it usually coincided with feelings of nausea. The most affected subjects showed a marked reluctance toward repeating the yohimbine test. Apparently the anxiety and fear induced by the drug remained clearly in the subjects' mind, which is in keeping with the observation that the drug did not cause confusion.

Premedication with amobarbital sodium (see above) completely abolished all subjective sensations induced by yohimbine, and only slight restlessness was observed whilst the subjects were asleep. Ro 5—0690 also reduced feelings of anxiety and tension but not to the same degree as the amytal. Medication with imipramine greatly increased the severity of the psychic changes induced by yohimbine. The tremor and restlessness became so marked in several cases that it amounted to an acute panic. This potentiation from imipramine was such that even in previously unreactive subjects the response induced by yohimbine produced definite tremor, restlessness, tension and anxiety.

In a group of five schizophrenic subjects yohimbine was given intramuscularly three times per week in doses dependent on the degree of response produced in the individual patient (range 20—40 mg. per dose). Usually the dosage was eventually increased, as a degree of tolerance appeared to occur, but maximum was kept at 40 mg. Of these five subjects, two showed a minimal over-all response to the injections. One was a schizophrenic in a state of remission with some remaining apathy and lack of initiative. The other was an extremely withdrawn, anergic, unresponsive little man who did not speak spontaneously at all and would reply to questions in monosyllables. The only significant effect produced with yohimbine was restlessness, tremor and slight

anxiety-type response in the latter case. However, they both became more active, alert, outgoing and generally more responsive. The first case was released from the hospital after termination of medication, but this may have had no relation to the medication. The other patient did not maintain this change after cessation of yohimbine.

The other cases also become more active and mobile, but their behavior was more disturbed. One admitted to auditory hallucinations and sat about muttering. All three became grossly disturbed for a period of about one hour after each injection of yohimbine. They actively hallucinated, laughed and addressed their hallucinations loudly, and made fists and threatened imaginary people and objects. This acute response completely subsided in the latter part of the day and they were then more alert, active and responsive than usual and a little euphoric. These effects were no longer present the next day.

The one depressive case studied showed initially a classic picture of endogenous depressive psychosis. He was inactive, hypochondrial, self-deprecatory and nihilistic. His speech was very retarded, and at times he was almost mute. After about one week on treatment his depression became definitely less severe, sleep improved, conversation was freer, and he was less nihilistic. But towards the end of the second week his condition was again approximately the same as at the commencement of treatment. He then progressively became worse, which necessitated discontinuance of yohimbine. At the end of the third week his condition was one of severe agitated depression with suicidal thoughts. E. S. T. was instituted, and significant improvement resulted but inadequate for release to be even considered.

Discussion

It should be pointed out that the methodology employed in this study is in several respects different from that used in most of the established autonomic drug tests. In the procedures suggested by FUNKENSTEIN et al. (1950) and by HOFFER and CALLBECK (1959b), epinephrine is given in a rapid intravenous injection, and methacholine and atropine have been given by the intramuscular route, all drugs in fixed standard doses. These procedures do not control for variable absorption from the i. m. route, dosage is not corrected for body weight, and, finally, speed and rate of intravenous injection are not defined. Age is a further factor which has been shown to be of importance (NELSON and GELLHORN) but is usually not controlled. On the basis of the findings with two different drugs, FUNKENSTEIN classifies his cases into categories which seem rather arbitrarily constructed without regard for the fact that the epinephrine *per se* does not seem to contribute to the resulting correlations (FUNKENSTEIN et al. 1952). For correlation with

these categories such complex factors as clinical diagnosis and the out-
come of E.C.T. and other treatments have been chosen. More recent
studies have questioned the reliability of these methods (MAAS; JANG)
and furthermore have failed to substantiate many of the original find-
ings (SLOANE et al.; LUNDE et al.; HOFFER and CALLBECK 1959a;
SATTERFIELD; OZTURK et al.; BRAUN and RETTEK; BRILL et al.).

The experimental procedure adopted in this study is so designed as
to control for the variables of body weight, absorption, and speed of
administration. Possible correlations with age are checked. Also, we
attempt correlation only between the actual quantitative responses
obtained and the rating of a single fairly well-defined clinical variable,
viz. the overall emotional reactivity. In individual cases observer error
may introduce an inaccuracy in rating. Over a series of 60 cases, however,
these random variations should cancel and allow an accurate assessment.
There are no signs of correlation between test results and diagnosis,
and no attempt is made at correlating test results with prognosis
which is a still more complex factor. A direct comparison between our
results and those of the FUNKENSTEIN group is not possible.

The effects produced by yohimbine are both adrenergic and cholin-
ergic in nature. Flushing, sweating, salivation, lachrymation, urgency
and frequency of micturition and defecation can likewise be produced
by intravenous metacholine and may be considered to be predominantly
cholinergic effects; whereas mydriasis, blood pressure increase, and
perhaps tremor and tachycardia may be considered to be adrenergic
type responses.

The usual psychic effect produced by yohimbine in our subjects was
an anxiety-type state. Similar effects have been reported from injected
epinephrine, and the utilization of such drug-induced psychic responses
has been investigated by other workers (LINDEMANN and FINESINGER;
FUNKENSTEIN et al. 1950). The anxiety response from yohimbine is,
however, much greater than with epinephrine. Similar type responses
may occur with other sympathomimetic amines (IVY and KRASNO) and
with the indole alkaloid ibogaine (SCHNEIDER and SIGG). These effects
of yohimbine are, therefore, certainly of central origin.

The adrenolytic properties ascribed to yohimbine in the literature
(RAYMOND-HAMET; BARRY; YONKMAN et al.; BOVET and BOVET-NITTI;
NICKERSON; GOODMAN and GILMAN) were not observed in our study.
This is most likely due to the much larger dosages (minimum 2—7,
usually 15—30 mg/kg) employed in the animal studies compared to
our dosage of 0.5 mg/kg. JANG (1941) using very low concentration
of yohimbine showed that it sensitized the perfused rabbits' ear to
epinephrine. A similar phenomenon was also observed in our study

in that both the heart rate effects, tremor and psychic actions of epinephrine were markedly potentiated by a previous yohimbine dose.

The central nervous system depressants and stimulants studied inhibited and potentiated, respectively, both the autonomic and the psychic effects of yohimbine. This supports the view that the yohimbine effects are to a great extent centrally mediated (cf. BOVET and BOVET-NITTI). This applies to all the effects of yohimbine except the rise in blood pressure, which was only partially reduced by premedication with amytal.

The degree of autonomic and psychic responsiveness to yohimbine was shown in three separate populations to be correlated with the basic emotional reactivity, irrespective of diagnostic category, of age and body weight. Of the autonomic measures, this responsiveness is reflected most accurately in the heart rate but not to any significant degree in the blood pressure. This test procedure can, therefore, give an index of responsiveness of the centers of emotional and autonomic reactivity in the thalamo-hypothalamic area.

Yohimbine was also found to activate the more or less latent psychotic process in some of our schizophrenic subjects. There was an increase in general reactivity, active hallucinations, expression of delusions and demonstrations of disturbance in behavior. Two other indole alkaloids, ibogaine and harmine, have been reported to have psychotomimetic effects with the production of excitement, inebriation states, mental confusion and hallucinations. All three indole alkaloids show distinct central nervous system stimulant properties. As regards ibogaine, the findings indicate involvement of cholinergic mechanisms in the production of central stimulation (SCHNEIDER and SIGG). However, it is difficult to ascribe all the effects of yohimbine solely to the cholinergic effects, as adrenergic stimulation is obviously also involved. This may account for the differences seen with these two compounds although there is a basic similarity in their effect.

Our findings indicate that yohimbine has marked autonomic and psychic effects which can be utilized for further studies. The almost specific anxiety-like response induced by yohimbine and its relationship with the basic level of emotional reactivity of the subjects is also of interest for further studies. Further, in psychotic subjects, excluding very chronic deteriorated subjects, yohimbine seems to produce activation of the psychotic picture. It would be of interest to study its effect on latent schizophrenic reactions. It is felt that studies with this compound may be especially useful in studying the problem of reduced autonomic and emotional responsiveness in deterioration of diverse origins. It may be helpful in elucidating relationships between emotional phenomena and autonomic responses in normal and mentally ill subjects.

Summary

Yohimbine in a dose of 0.5 mg/kg has been given to 51 male mental hospital subjects and nine normal volunteers.

It has produced both cholinergic and adrenergic-type autonomic effects and psychic effects simulating an anxiety state. The degree of both these responses to yohimbine correlates highly with the basic level of emotional reactivity.

Central nervous system depressants, amobarbital and Ro 5—0690, reduced the degree of response to yohimbine, whilst the CNS stimulants imipramine and epinephrine potentiated the yohimbine effect. Yohimbine in the dosage here employed did not have any blocking effect against injected epinephrine.

Activation of the psychotic picture was produced by yohimbine in some schizophrenic cases.

Yohimbine is a promising compound for use as an autonomic test drug.

References

ACKNER, B., and G. PAMPIGLIONE: An evaluation of the sedation threshold test. J. psychosom. Res. **3**, 271—281 (1959).

BARRY, D. T.: Some features of the pharmacological actions of yohimbine and ergotamine. Arch. int. Pharmacodyn. **55**, 385—401 (1937).

BOVET, D., et F. BOVET-NITTI: Médicaments du système nerveux végétatif. Basel and New York: Karger 1948.

BRADLEY, P. T., and P. M. JEAVONS: The effect of chlorpromazine on sedation and convulsive thresholds in schizophrenic patients. Electroenceph. clin. Neurophysiol. **9**, 661—682 (1957).

BRAUN, M., and S. RETTEK: A study of the value of the Funkenstein test as an indicator of the effectiveness of ataractic drugs. Amer. J. Psychiat. **116**, 66—67 (1959).

BRILL, N. Q., E. CRUMPTON, S. EIDUSON, H. M. GRAYSON and L. I. HELLMAN: Predictive and concomitant variables related to improvement with actual and simulated ECT. A.M.A. Arch. gen. Psychiat. **1**, 263—272 (1959).

DOUGLAS, D. B., and P. H. HOCH: Blood pressure studies in schizophrenia: Atropine and saline. Psychiat. Quart. **30**, 204—210 (1956).

FUNKENSTEIN, D. H., M. GREENBLATT and H. G. SOLOMON: A test which predicts the clinical effects of electric shock treatment on schizophrenic patients. Amer. J. Psychiat. **106**, 889—901 (1950).

— — — An automatic nervous system test of prognostic significance in relation to electroshock treatment. Psychosom. Med. **14**, 347—362 (1952).

GOODMAN, L. S., and A. GILMAN: The pharmacological basis of therapeutics. New York: Macmillan & Co. 1958.

GROSZ, H. J., and I. MILLER: Two factors limiting the reliability of the Mecholyl test: Variability in day-to-day responses and dissimilarity between simultaneous determinations. J. nerv. ment. Dis. **127**, 417—429 (1958).

HOFFER, A.: Effect of atropine on blood pressure of patients with mental and emotional disease. A.M.A. Arch. Neurol. Psychiat. **71**, 80—86 (1954).
—, and M. J. CALLBECK: Prognostic value of the Mecholyl test. Dis. nerv. Syst. **20**, 209—210 (1959a).
— — Differential response of schizophrenic and other psychiatric patients to atropine. Dis nerv. Syst. **20**, 387—390 (1959b).
HOLMBERG, G., and S. GERSHON: Yohimbine as an autonomic test drug. Nature (in press).
IVY, A. C., and L. R. KRASNO: Amphetamine (Benzedrine) sulphate. A review of its pharmacology. War Med. (Chicago) **1**, 15—42 (1941).
JANG, C. S.: The potentiation and paralysis of adrenergic effects by ergotoxine and other substances. J. Pharmacol. exp. Ther. **71**, 87—94 (1941).
KENDALL, M. G.: Rank correlation methods. London: Griffin 1948.
LINDEMANN, E., and J. E. FINESINGER: The effect of adrenaline and mecholyl in states of anxiety in psychoneurotic patients. Amer. J. Psychiat. **95**, 353—370(1938).
LUNDE, F., E. MANSFIELD and J. A. SMITH: Mecholyl chloride as a prognostic test in psychiatric patients. J. nerv. ment. Dis. **127**, 430—436 (1958).
MAAS, J. W.: Reliability of the metacholine (Mecholyl) test. A.M.A. Arch. Neurol. Psychiat. **79**, 585—589 (1958).
MYERSON, A., J. LOMAN, and W. DAMESHEK: Physiologic effects of acetyl-beta-methylcholine (Mecholyl) and its relationship to other drugs affecting the autonomic nervous system. Amer. J. med. sci. **193**, 198—214 (1937).
NELSON, R., and E. GELLHORN: The influence of age and functional neuropsychiatric disorders on sympathetic and parasympathetic functions. J. psychosom. Res. **3**, 12—26 (1958).
NICKERSON, M.: The pharmacology of adrenergic blockade. Pharmacol. Rev. **1**, 27—101 (1949).
OZTURK, O. M., A. O. BATTLE and G. H. AIVAZIAN: On the epinephrine-Mecholyl test. Dis. nerv. Syst. **20**, 250—253 (1959).
RAYMOND-HAMET, C. R.: Sur un nouveau cas d'inversion des effets adrénaliques. C. R. Acad. Sci. (Paris) **180**, 2074 (1925).
SATTERFIELD, H. J.: Prediction of improvement by use of epinephrine-metacholine (Mecholyl) test. A.M.A. Arch. Neurol. Psychiat. **81**, 513—516 (1959).
SCHNEIDER, J. A., and E. B. SIGG: Neuropharmacological studies on ibogaine, an indole alkaloid with central-stimulant properties. Ann. N.Y. Acad. Sci. **66**, 765—776 (1957).
SHAGASS, C.: The sedation threshold. A method for estimating tension in psychiatric patients. Electroenceph. clin. Neurophysiol. **6**, 221—233 (1954).
—, and J. NAIMAN: The sedation threshold as an objective index of manifest anxiety in psychoneurosis. J. psychosom. Res. **1**, 49—57 (1956).
SLOANE, R. B., D. J. KEWUS and P. SLATER: Prognostic value of adrenaline and mecholyl responses in electroconvulsive therapy. J. psychosom. Res. **2**, 271 to 273 (1958).
THORPE, J. G., and J. C. BARKER: Objectivity of the sedation threshold. A.M.A. Arch. Neurol. Psychiat. **78**, 194—196 (1957).
YONKMAN, F. F., D. STILWELL and R. JEREMIAS: The adrenolytic and sympatholytic actions of yohimbine and ethyl yohimbine. J. pharmacol. exp. Ther. **81**, 111—115 (1944).

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