ELECTROENCEPHALOGRAPHIC AND BEHAVIORAL EFFECTS OF TOFRANIL

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ELECTROENCEPHALOGRAPHIC AND BEHAVIORAL EFFECTS OF TOFRĀNIL

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With the rapid increase in the number of potential psychopharmaceuticals, the need for screening technics has become more acute. In studies of the electrographic patterns of convulsive therapy, the hypothesis evolved that behavioral changes induced by new compounds could be related to their neurophysiologic effects as reflected by the type and degree of electrographic change (1, 2). This suggestion followed a similar one by Wikler (3) who stated that "regardless of the nature of the drug administered, shifts in the pattern of the electroencephalogram in the direction of desynchronization occurred in association with anxiety, hallucinations, fantasies, illusions or tremors, and in the direction of synchronization with euphoria, relaxation or drowsiness." Studies with various psychotropics (4) and anticholinergic hallucinogens (5, 6) supported such a relationship. It is the purpose of this preliminary report to describe initial behavioral and electrographic observations with Tofrānil†, a new psychopharmaceutical, and to relate these observations to the neurophysiologic-adaptive hypothesis of the mode of action of physiodynamic therapies (1).

Methods

Two types of studies were undertaken in an open-ward, voluntary hospitalized population. In 28 acute experiments, consecutive patients referred for physiodynamic therapies were tested in the EEG laboratory at various stages of treatment. Tofrānil solution (10 mg/ml) was administered intravenously at a set rate (1 ml/40 sec.) until electrographic or behavioral changes became prominent, for a total of 40-125 mg (0.5-mg/kg). Behavioral observation and electrographic recording continued for one to three hours.

A second group of 16 patients manifesting depressive, withdrawn or retarded behavior were referred by their therapists for pharmacotherapy. The patients received daily oral Tofrānil, 75-250 mg. Behavioral observations and EEG recordings were made prior to and during treatment. Patients ranged in age from 17 to 58, and were diagnosed as suffering from schizophrenia, manic-depressive and involutional depressive psychoses, and psychoneuroses.

Observations

1. *Acute Studies:* On acute administration, there was an initial restlessness, associated with dizziness, dry mouth, "faintness," nausea, and on four occasions, vomiting. These symptoms persisted for 10-20 minutes, and were accompanied by lassitude, heaviness of the extremities and eventual drowsiness. Heart rate was unchanged or slowed. Subsequently, subjects were relaxed, quiet and disinclined to activity, even when returned to their ward.

The electrographic patterns accompanying these behavioral changes were initiated by a gradual decrease in voltages during the injection. By ten minutes, the per cent time alpha and mean alpha voltage had been halved. In four patients with moderate amounts of beta activity, such activity increased in voltage and per cent time. By twenty minutes, in association with behavioral lassitude, low voltage (to 50 microvolts) random theta frequencies (5-7 cps) appeared (Figures 1 and 2).

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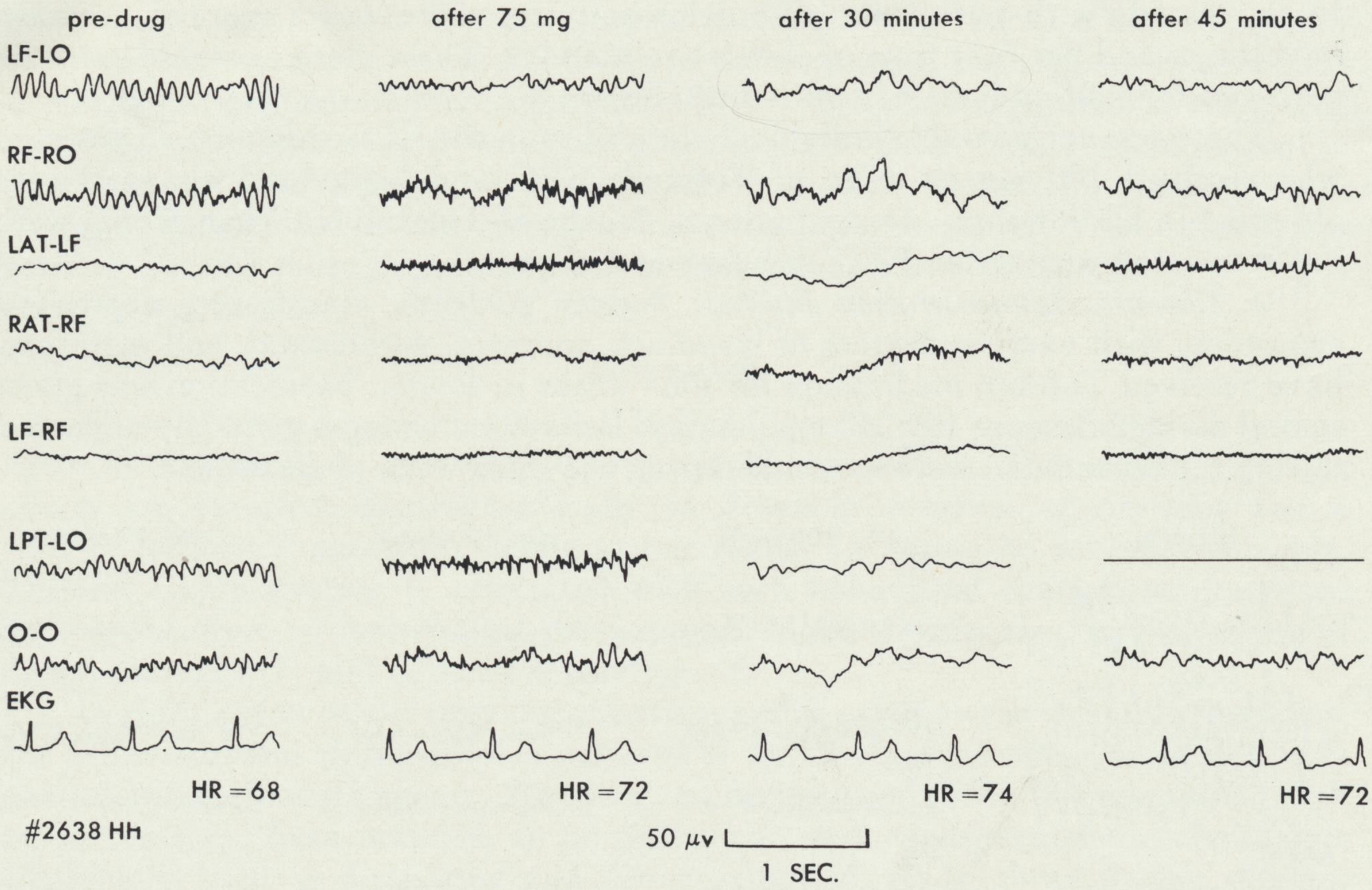

Fig. 1
Effect of intravenous Tofrānil on EEG delta
(female, aged 46)

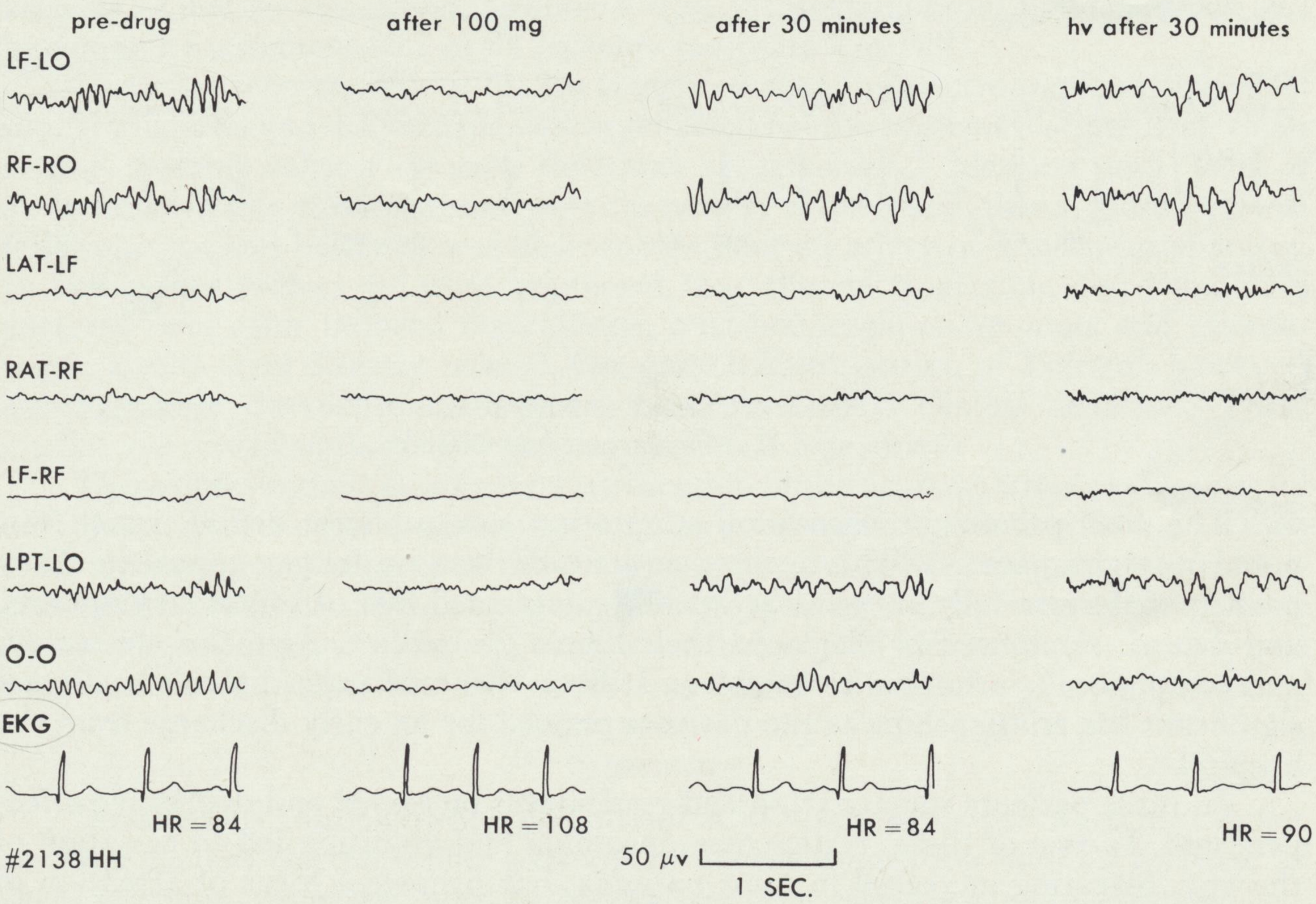

Fig. 2
Effect of intravenous Tofrānil on EEG delta
(male, aged 37)

In six records with post-convulsive delta activity, there was a marked decrease in voltages and per cent time of slow wave activity. These electrographic patterns persisted for half-an-hour to two hours (Figure 3).

There was considerable individual variability in the EEG response. In patients who received 100 mg or more of Tofrānil, EEG and behavioral changes were observed in all but three. In six patients, dosage of Tofrānil less than 50 mg were not associated with either EEG or behavioral changes.

2. Chronic Administration Studies: Sixteen patients, manifesting depressive symptoms with varying degrees of insomnia, anorexia, withdrawal, and agitation, have received Tofrānil medication for four weeks or longer. Medication was given in oral divided doses of 100-250 mg per day. Behavioral changes generally appeared during the second and were maximal during the third week of treatment.

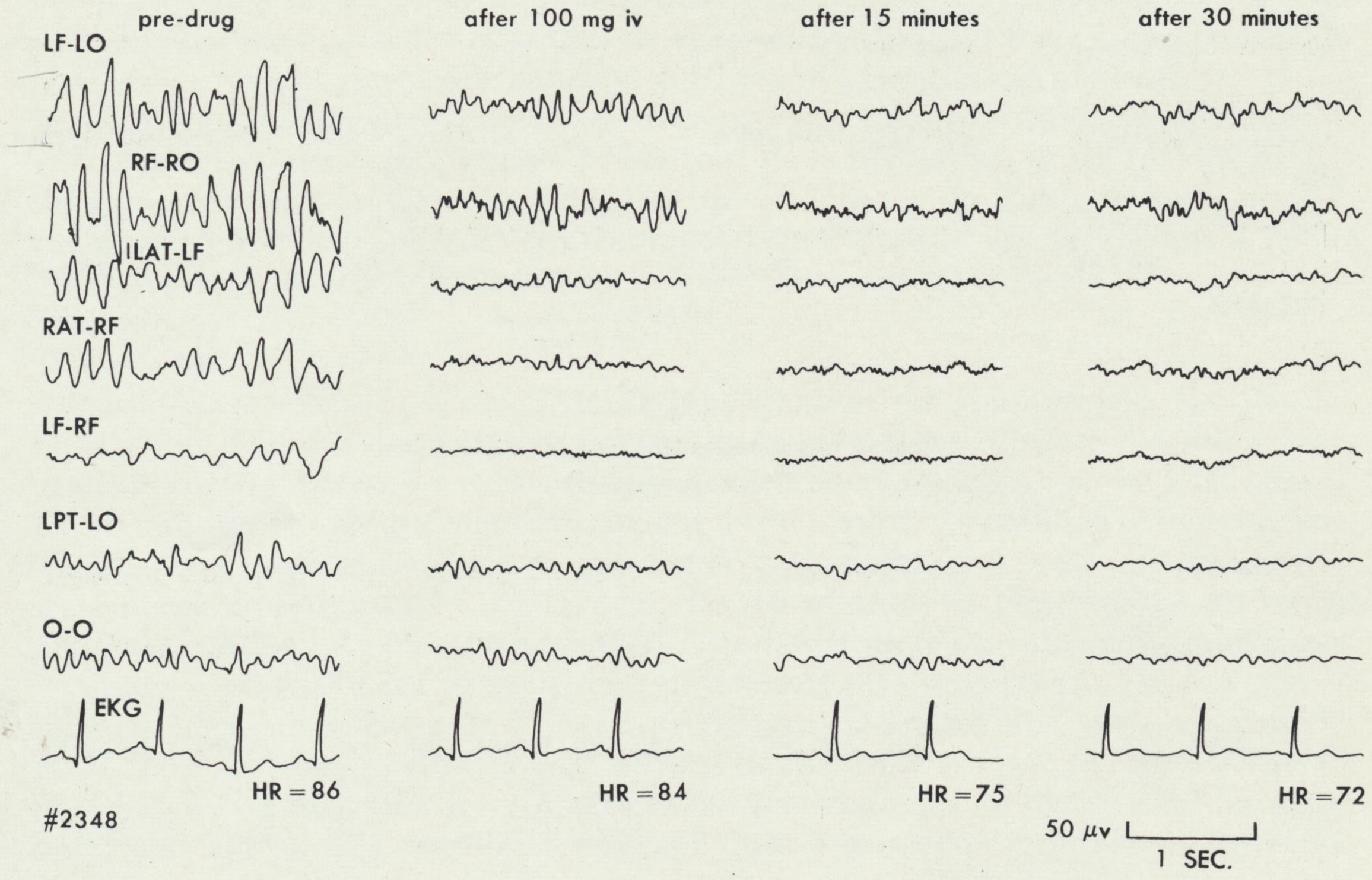

Fig. 3
Effect of Tofrānil on EEG delta
(female, aged 41: 24 hours post convulsion no. 7)

The most prominent behavioral adaptation was euphoric denial, which was noted in eight patients. The depressive attitude was no longer apparent. They participated more fully in ward activities, complained less of somatic symptoms, and denied, minimized or displaced their illness on inquiry. Agitation decreased, and complaints of insomnia became less. It became increasingly difficult to discuss significant life relationships as the patients pressed for an early discharge from the hospital.

In three patients somatization and restlessness increased and depressive affect persisted. In two of these, restlessness, insomnia and vomiting led to cessation of therapy. Sweating increased in most patients, but became a focus of attention in these subjects.

No change in symptoms were noted in five patients after four weeks of therapy.

While no serious complications of therapy were noted, nausea, increased sweating, vomiting, dryness of the mouth, restlessness and excitement, and increasing

insomnia were reported. These were prominent early in therapy, and except for the vomiting and restlessness, did not limit the treatment. In three subjects medication was initially administered parenterally without untoward effects. Abnormal motor patterns and seizures were not noted in these patients at these dosages.

Electrographic studies on chronic administration showed minimal changes. Voltages became lower and record modulation became poorer. Well-defined fast activity became more prominent, and in four subjects low-voltage theta (5-7 cps) activity was noted.

Discussion

These observations indicate that Tofrānil is an active central nervous system agent in man, both on oral and intravenous administration. The neurophysiologic effects are manifest electrographically as desynchronization of rhythms and a shift in frequency spectrum to the slower range. In depressed retarded subjects, Tofrānil administration is associated with such behavioral changes as decreased depressive affect with increased participation in ward activities, increased use of denial patterns (7) and occasional excitement.

In comparison to our previous experience with other physiodynamic therapies, the behavioral and electrographic patterns of Tofrānil are most like those seen with central anticholinergic agents. We observed desynchronization of frequencies, with an increase in theta activity, to be prominent with experimental anticholinergic compounds such as diethazine and benactyzine* (5, 6). In those studies, electrographic desynchronization was associated with behavioral alerting, excitement and illusory and hallucinatory activity. On Tofrānil administration, similar electrographic patterns of desynchronization were observed, accompanied by euphoria and increased ward participation. While we have not observed hallucinatory activity at our dosage ranges, Lehmann *et al.* (9) have reported hallucinations and hypomanic excitement in 7 of 84 patients receiving Tofrānil.

In earlier reports, Wikler (3, 10) suggested that the electrographic patterns of synchronization and desynchronization reflected neuron systems distinct from those neuron systems subserving such functions as 'sensation,' 'ideation' and 'level of awareness.' While these systems were frequently interlocked, dissociation between EEG pattern and behavior was observable under a variety of drug-induced states. In our earlier studies we were impressed that the electrographic and behavioral patterns seen after induced convulsions, anticholinergic compounds and phrenotropic agents were directly related. On acute administration of Tofrānil, however, electrographic desynchronization was associated with clinical sedation. These studies are consistent with Wikler's suggestion.

These observations permit the classification of the neuropharmacologic activity of Tofrānil in the central nervous system as predominantly anticholinergic. However, we have noted aspects of the electrographic and behavioral patterns reminiscent of increased cholinergic activity. These include the electrographic shift to slower frequencies and sedative, euphoriant behavioral effects. Such observations suggest that there may also be an effective degree of central cholinergic activity.

Summary

Intravenous administration of Tofrānil in 28 voluntary, open-ward psychiatric patients elicited electrographic patterns of desynchronization and an increase of theta rhythms, associated with behavioral alerting, relaxation and lassitude.

Chronic administration of oral Tofrānil in 16 depressed and retarded psychiatric subjects elicited behavioral adaptations of euphoric denial in eight, restlessness

*A recent report by Abood and Meduna (8) relates the behavioral improvement in depressed patients with JB-329, a new central anticholinergic agent which has similar electrographic patterns.

and somatization in three and no change in five. During the fifth week of administration, electrographic desynchronization was manifest.

It is concluded that Tofrānil is an active central nervous system agent, with a spectrum of activity most like experimental anticholinergic hallucinogens. The theoretic significance for neurophysiologic-behavioral constructs is briefly discussed.

Résumé

Nous avons étudié la relation existant entre les effets du Tofrānil sur le comportement et sur le tracé électrographique, chez des patients atteints de psychoses aiguës ou chroniques.

Méthode

Cas aigus: les patients retenus étaient examinés avant le traitement physiodynamique, ainsi qu'à divers stades de celui-ci. Le Tofrānil était administré en injections intraveineuses d'une solution à 10 mg/ml, jusqu'à un total de 40-125 mg (0,5-2,5 mg/kg), concurremment avec des examens électro-encéphalographiques.

Cas chroniques: des patients présentant de la dépression et un ralentissement du comportement étaient mis à la dose de 75-250 mg de Tofrānil par jour. Les examens encéphalographiques et du comportement étaient effectués avant le début du traitement, et à intervalles d'une semaine au cours de celui-ci.

Observations

1° Cas aigus

a) *Comportement:* au cours de l'administration du médicament, sur 28 cas, nous avons noté des nausées, des vertiges et de la faiblesse. Quatre fois des vomissements sont survenus. Le rythme cardiaque est demeuré inchangé, ou s'est ralenti. En 10 minutes ces symptômes diminuaient d'intensité et les patients se détendaient.

b) *Electro-encéphalogramme:* pendant le traitement, il y a eu une diminution du voltage dans toutes les fréquences. En 10 minutes le pourcentage de temps alpha baissait et les voltages tombaient à la moitié de leurs valeurs initiales. Chez les sujets à activité bêta (4 cas), celle-ci devenait plus importante. Au bout de 20 minutes, des ondes lentes de 5-7 cps, atteignant 50 microvolts, apparaissaient ici et là. Dans les enregistrements avec activité delta postconvulsive (6 cas) nous avons noté une baisse marquée des voltages et des pourcentages de temps dans l'activité des ondes lentes. Ces tracés électrographiques persistaient pendant ½-2 heures.

2° Cas chroniques

a) *Comportement:* seize sujets ont été observés à ce jour. Les effets initiaux de la médication furent des nausées, des vomissements, de l'agitation et de l'excitation, une exagération de l'insomnie et une transpiration très augmentée dont se plaignaient les malades. Le traitement a été interrompu dans deux cas avec agitation. Des 13 autres sujets, 6 ont vu leurs symptômes de dépression s'amender et ont pu reprendre une plus grande activité; ils ont pu être renvoyés chez eux, ou ont été prévus pour un prochain licenciement. Les autres n'ont guère présenté de changements dans leurs symptômes, ou n'ont été soumis à la thérapeutique que pendant un temps trop court.

b) *Electro-encéphalogramme:* Les enregistrements obtenus pendant le traitement n'ont montré que peu de modifications. Leur modulation était appauvrie et leurs voltages abaissés. Une activité rapide bien caractérisée a pris de l'importance; chez 4 malades nous avons noté une activité à bas voltage de 5-7 cps.

Conclusions

1° Chez les psychopathes, les effets electrographiques du Tofrānil sont une désynchronisation, suivie par une activité d'ondes lentes à bas voltage. Ces tracés sont moins prédominants dans les cas chroniques traités, et ressemblent alors à ceux que l'on obtient avec la benactyzine.

2° En ce qui concerne le comportement, nous constatons une augmentation de la motilité, un changement dans l'humeur et un malade plus éveillé.

3° Ces observations concordent avec les hypothèses neuro-physiologico-adaptatives expliquant le mode d'action des traitements physiodynamiques des psychoses.

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General discussion from the floor (summarized)

The question was asked whether administration of a large dose of Tofrānil once a day would not be as effective as multiple dosage. This would of course be a tremendous saving in the time of the nurses involved. In answer it was stated that Tofrānil is best given not in one large daily dose but in a series of small doses such as 2 tablets t.i.d. It was also brought out that Tofrānil has a tremendous influence on transference phenomena and that these can be analyzed in dreams and symbolisms. While such observations have been made, definitive results must await an extensive study.

Another discussant asked what is the difference between the effect of barbiturates and anticholinergic drugs on the EEG.

One discussant felt that the EEG was a poor tool, since it could be modified in only two ways, synchronization or desynchronization, and firm conclusions should not be drawn from such changes. He therefore felt that analogies between diethazine and Tofrānil were dubious and that nausea was not a specific effect of Tofrānil. He wondered if EEG changes would always exist in the absence of nausea, and felt it important to correlate EEG changes with clinical changes.

In replying to these comments, Dr. Fink stated that he considered Tofrānil an anticholinergic drug because of its similarity to other anticholinergic drugs in regard to its EEG patterns. Dr. Fink recalled that Dr. Sigg's paper had also indicated that Tofrānil was an anticholinergic drug. Many anticholinergic compounds appear to have rather specific central effects, and some are also experimental hallucinogens. In his experience, barbiturates produce not desynchronization, but rather synchronization. This becomes clear if the factors of dosage and time are considered. Thus the initial effect is hypersynchronization; if the drug is continued, sleep is of course produced and the initial effect disappears.

The author replied to the criticism of his use of EEG. He agreed that it is a poor tool in many respects, but that it is possible to analyze EEG records for synchronization, desynchronization and frequency shifts. One obtains different patterns with different agents even in the same patient. Dr. Fink explained that he was making a long-term study, and hoped that more conclusive data could be offered at a later time.

EEG and Behavioral Effects of Tofranil

Max Fink, M.D. *

The relation between the electrographic and behavioral effects of Tofranil in voluntary psychiatric patients was determined in acute and chronic studies.

Method:

Acute: Consecutive patients referred for physiodynamic therapies were tested prior to and at various stages of therapy. With EEG recording, Tofranil solution (10 mg/cc) was administered intravenously for a total of 40-125 mg (0.5-2.5 mg/kg).

Chronic: Patients manifesting depressive and retarded behavior were placed on regimens of 75-200 mg Tofranil daily. EEG examinations and behavioral observations were made prior to and at weekly intervals during treatment.

Observations:

1. Acute Studies:

a. Behavior: During drug administration in 25 subjects, nauseau, dizziness and weakness were reported. Vomiting occurred on four occasions. Heart rate was unchanged, or slowed. In ten minutes, these symptoms were less, and patients were relaxed.

b. EEG: During administration there was a decrease in voltage of all frequencies. By ten minutes, the per cent time alpha decreased, and voltages were half of the initial values. In patients with moderate amounts of beta activity (4), such activity became more prominent. By twenty minutes, slow wave activity of 4-7 cps, up to 50 microvolts appeared randomly. In records with post-convulsive delta activity (6), there is a marked decrease in voltages and in per cent time of slow wave activity. These electrographic patterns persisted for ½ - 2 hours.

2. Chronic Studies:

a. Behavior: Fifteen patients have been under observation to date. Initial effects of medication included nausea (8), vomiting (2), restlessness and excitement (2), insomnia exaggerated (3), and complaints of excessive sweating (11). In the two patients with restlessness, medication was discontinued. Of the thirteen patients, six manifested an alleviation of symptoms of depression with increased participation in activities, and have been discharged or recommended for discharge. The remaining patients have shown little change in symptoms (3) or therapy has been administered for too short a period (4).

b. EEG: In records obtained during treatment, minimal changes were observed. Modulation of records was poorer with lower voltages. Well defined fast activity became more prominent; and in four subjects low voltage 5-7 cps activity was noted.

Conclusions

1) Electrographic effects of Tofranil in psychiatric patients are those of desynchronization, followed by low voltage slow wave activity.

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These patterns are less prominent on chronic administration, and resemble those of benactyzine.

2) Behavioral effects are those of alerting, mood change and increased motility.

3) These observations are consistent with the neurophysiologic-adaptive hypothesis of the mode of action of physiodynamic therapies of psychoses.