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Tranquilizers: Experimental Proof for their Specific Effects[1]

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I FEEL listless and tired . . . I do not care . . . I don't want to do anything, even to change the position of my body, I just want to be left in peace and lie quiet." "The next day it took a special decision to talk to somebody. If a person came to ask me something I got annoyed and tried to get away from him as soon as possible, because talking meant a special effort. And my dry mouth was not the only reason for this. There was a tendency to sit and stare into space—let things take their own course. I had to exert myself to follow a lecture. And when I attended the conference afterwards I had to make up my mind again and again about the difficult decision whether to take part in the discussion. At the same time I believed that I was able to remember things normally and understand them, but there was a reluctance to make decisions, to start something, or face any problems. This became prominent when I started to deal with my correspondence. I had three letters in front of me all dictated by a colleague. After signing the first one I mechanically put my name to the second one though I did not agree with it and knew distinctly that it would have to be rewritten. Two hours later, when the drug effect had diminished, I was terrified by what I had done and had to go through a lot of complicated procedures until I had traced and recovered the letter." "At about 5.40 p.m. I drove my car through the rush hour traffic across the city. I felt wretched, was dead tired, and was surprised that no accident happened. The driving, however, went very well. After that I had my supper in company where every action like passing a dish seemed like a momentous decision. The decision once taken, it did not need a special effort to execute it. Afterwards I was working with somebody on the translation of a paper into a foreign language. In the discussion about certain renderings I recognized a tendency in me to give in, not really caring how it would sound in the end. There was only one wish predominant, to get things over with . . . At 8.30 p.m. I went to bed and slept for 10 hours (unusually long) until I awoke in the morning. I still felt apathetic and there was a kind of veil in front of my face. I noticed that everyday actions like shaving, once they were started, were completed without any effort. The difficulty consisted in taking the decision to start anything. . ."

The foregoing are excerpts of three descriptions by persons who had taken 37.5 mg of chlorpromazine (Thorazine) for experimental purposes, this being the most thoroughly investigated and probably most widely used of the group of drugs called "tranquilizers". The authors of this paper (H. Heimann, P. N. Witt, 1955) had observed 12 healthy subjects before and after they had taken the drug. They had experienced some difficulty in summarizing the diversity of experiences and symptoms encountered in the different subjects. They tried to establish one general pattern of changes which then might be called characteristic for the drug. The listlessness, fatigue and frequently mentioned feeling as if a veil was drawn in front of the eyes reminded the participants of the effect of sedatives and sleeping drugs. A cancellation test showed that while control persons improved their performance with each repetition, people who had taken chlorpromazine did not change, staying just as slow as the first time. This could not

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be attributed to any impairment of learning because the speed of correct cancellation in the first two lines of the test increased equally for controls and drug subjects. Those that had taken chlorpromazine, however, slowed down significantly during the later part of each test while controls kept up their initial speed. It showed that endurance or the ability to keep up the speed of a performance over several minutes was impaired.

There was a distinct sequence of chlorpromazine effects apparent. Autonomous disturbances like a dry mouth, dry eyes, congestion of nose and face in the initial 30 minutes were followed by nearly 24 hours of behavioral changes like apathy, sleepiness and lack of drive. This, however, changed if you gave a different tranquilizer like reserpine (Serpasil) or meprobamate (Miltown). Did all these drugs have something special in common? Is the tranquilizer just another sleeping drug with a relatively wide margin between the sedative dose and that which produces sleep? Freyhan (1959) and several investigators with him object to the group name tranquilizers because "this classification is psychologically too seductive, pharmacologically too unspecific, and in terms of results not infrequently untrue." Klerman et al. (1960) had a similar concept in mind when they tested whether a clinically effective dose of a tranquilizer, even in a prolonged course of pharmacotherapy, could moderate anxiety and truly "sedate" without impairing significantly intellectual performances, coordination, and perception. They gained the impression that the tranquilizers meprobamate and reserpine in doses used clinically could induce a feeling of relaxation without concomitant drowsiness or psychomotor retardation. Secobarbital and phenyltoloxamine, in contrast, could not be used without producing marked drowsiness. So they came to a conclusion slightly different from Freyhan which they define as follows: "In assessing the actions of a number of psychopharmacological agents during double-blind studies on normal human subjects, observations were made bearing on the nature of sedation and tranquilization as psychophysiological states. Data were presented to indicate that sedation and tranquilization are similar states. It was concluded that the special *properties* of so-called "tranquilizer" drugs do not lie in their ability to induce a unique psychic state different from sedation, but, rather, lie in the dosage margins between their sedative effects and their effects on psychomotor performance, consciousness, and physiological functions." "The wide dosage margin between the sedative and hypnotic actions of the new drugs is also associated with different dose thresholds for effects upon psychomotor agitation and pathological mood. It appears that the different actions of the newer drugs occur at different dose thresholds. With the newer drugs, certain effects, previously occurring simultaneously, are dissociated from each other, becoming manifest at different doses." These workers seem to visualize tranquilizers as sedatives where the different stages of the drug effect are spread wider apart than in our older sleeping drugs. By adjusting the dose carefully it should be possible, according to such a view, to tranquilize with a barbiturate in a narrow low dose range or produce sleep and anesthesia with a high dose of a tranquilizer. I think we have proof now that this is not so.

I intend to bring evidence from animal experiments done in several pharmacological laboratories including our own which will answer the questions raised here. The experimental results obtained will open our eyes to the specific effects of tranquilizers in the areas where they differ from sleeping drugs. Evidence will be presented to show that they have some common properties. Our considerations do not affect the differences in side effects of the various tranquilizers which have been well documented in experimental and clinical statistics.

Let us look together at a series of behavioral experiments (Brettschneider et al., 1959): A group of 40 young Sprague-Dawley rats was handled and petted every day. They were also put regularly on a knotted rope hanging from a

pole into a transparent plastic cage. This taught them to climb up and down the rope into and out of the cage. They eventually lost their tense and fearful behavior and began to explore the cage and climb the rope. The training proper began a few weeks after these preparations. A bright light, easily visible through the plastic walls of the cage, was flashed for one second. This was followed two seconds later by an electric shock through the grid floor of the cage. The sequence was repeated once every ten minutes. While all rats tried to escape from the cage when the shock occurred, 50% of them learned very soon to avoid the shock altogether by climbing the rope after the light flashed. A little later no shocks had to be given any more. A number of individuals had changed from an unconditioned (shock) to a conditioned (light) avoidance behavior. The motivation for this behavior was fear or anxiety or both which had made them learn something. Only those rats were selected for the drug experiment which had performed satisfactorily on several days, i.e. climbed the rope not more than two seconds after the light had flashed. One, two or four mg/kg chlorpromazine was injected subcutaneously. This resulted in a suppression of the response, graded in time according to the dose given. It took the rats more and more time to climb the rope as the drug took its effect. As any response delayed more than 150 seconds was called negative, such a time interval is the upper limit of our measure or indicates complete suppression of the conditioned avoidance behavior. After 1 mg/kg suppression lasted for a few minutes, after 4 mg/kg half an hour. Rats put at this time on the ropes or on an inclined wire-mesh screen were well able to hold themselves up there. There was no indication of paralysis or diminished motor ability. They could climb but did not do it. It was not possible, however, to determine whether learning or the motivation to climb was diminished.

For comparison these same animals were injected with about equally effective doses of pentobarbital (Nembutal), namely 15 and 20 mg/kg. Such doses suppressed the rope climbing response only at a time when the animal was unable to hold itself on the rope or an inclined wire screen. To put it in descriptive terms: the sleepy and atactic rat, lying on its side, still tried to move in the direction of the rope as soon as the light flashed but did not succeed any longer in pulling itself out of the cage. The conclusion: motivation and/or learning were hardly affected by the barbiturate at a time when motor performance was severely impaired.

The question may be asked: What happens if the rat learns to leave the cage even before the light flashes? This actually occurred in a number of animals, and G. Maffii (1959) investigated the effects of tranquilizers and other agents on such a "secondary conditioned response". He gave the rats a trial every 30 minutes and termed two escapes in 15 seconds without light flash or shock a secondary conditioned response. Usually after 33 conditioning trials 90% of his rats had developed such a response and retained it. After 1.75 mg/kg chlorpromazine a 50% block of the secondary conditioned response occurred while the conditioned response was not impaired. Increasing the dose to 11.6 mg/kg resulted in 50% suppression of the conditioned response without noticeable impairment of the unconditioned response. Only after 33 mg/kg was the unconditioned response blocked and the rats did no longer try to leave the cage even after a shock.

A similar relationship of blocking first one response then the other held true for other tranquilizing agents such as promazine (Sparine), hydroxyzine (Atarax, Vistaril), azacyclonol (Frenquel), meprobamate (Equanil, Miltown) and phenaglycodol (Ultram). They have therefore been termed secondary or general deconditioning agents. For other drugs like mephenesin (Tolseram), glutethimide (Doriden) and some barbiturates the pattern was found to be different. Any dose which blocked the secondary conditioned response would affect the other two responses too. It seems that according to this nomenclature

only the tranquilizers of all the agents tested were "deconditioning agents".

It is difficult to interpret such results because the procedure of testing is complex. It is hard to define what we are testing. But even the simpler measurements of spontaneous activity in the so-called jiggle cage by Read et al. (1960) distinguishes between chlorpromazine and phenobarbital effects. For this test each mouse was kept in a cage which was mounted on a spring lever and a recorder measured the number of times the cage tipped and closed a microswitch. A control curve showed a slow decrease in spontaneous activity in the course of 80 experimental minutes. The average figure did not, however, go below 35 counts per 5 minutes. After the subcutaneous injection of 0.25, 0.5, and 1.0 mg/kg chlorpromazine activity declined immediately, the degree depending on the dose. With 0.25 mg/kg it began to recover after about 25 minutes, but not after the higher doses. In contrast, phenobarbital in the lowest dose (60 mg/kg) increased the activity during the 80 minutes experimental time. A high dose of 90 mg/kg first increased and later decreased activity. And even the highest dose of 120 mg/kg produced more than a 300% increase in counts before the mice went to sleep at the end of an hour, a distinct contrast to the behavior after chlorpromazine. The difference between the drugs was clearly not one of dosage because the stimulant effect of phenobarbital could not be produced with any dose of chlorpromazine.

The last behavioral test procedure to be discussed in this connection made use of the innate pattern of web-building behavior of spiders. Only those building two-dimensional orb-webs like Araneus diadematus Cl., the garden spider, were found suitable. The animals were kept in the laboratory in individual wooden frames 20 x 20 inches with glass sliding doors. Under favorable outside conditions they built a new web every morning after the the old one had been destroyed on the preceding afternoon. Experience has taught that drugs which affect behavior have a profound influence on the web patterns. A spider impaired in its movements by drugs like caffeine or d-amphetamine (Dexedrine) will still build a web (P. N. Witt, 1956). But such a web differs measurably from webs built on the preceding or following days. This can be proved by measuring the proportions of the webs on photographs. In order to obtain a good photographic contrast webs are made visible by spraying them with white paint. In a series of experiments each spider received 500 mg/kg pentobarbital (Nembutal) 7 hours before web-building time. All webs built the following morning were significantly different from control webs in the following proportions: 1) The catching area, represented by the area which is covered by the viscid spiral, was significantly decreased in size. 2) The webs were significantly longer than before drug application. This was calculated by dividing the horizontal diameter by the vertical diameter. 3) The angles between the radii of each web were significantly more irregular. This means that the difference between neighboring angles was increased. 4) The position of the hub in the web varied more than normal, being frequently far away from the geometric center of the nearly round catching area. 5) There was also a slightly increased number of oversized angles observed. Such angles are defined as being larger than the sum of their two neighbouring angles. All these changes had disappeared in the webs which were built one day later. In this test system chlorpromazine again caused a different kind of change. Graded according to dose, (100 mg—10 g/kg), a significant decrease in web-building frequency for one to three and more days appeared. After the highest dose only one animal built the next day and this web was slightly distorted. In all other instances if webs were built at all they were in the normal range of our control web measurements.

In order to understand such results a little better we must try to find out what makes the spider build a web. It is generally believed that hunger is the drive which determines the mood for web-building. More factors are needed to set the building process into motion

provided hunger has set the stage. There is good evidence that the early morning temperature rise after an overnight low together with the change from dark to light is involved in web-building. These two conditions are given simultaneously in the early morning hours at sun rise on a summer day. And the early morning is just the time at which all hungry spiders build their webs. Experiments carried out with spiders under constant light and temperature conditions have led to a significant decrease in web-building frequency in hungry spiders. The spiders which did not build after chlorpromazine could either not be hungry or their threshold for releasing the act of web-building had been raised in some other way. The latter seems more likely, because feeding experiments have shown that chlorpromazine spiders eat well, just as do patients under chlorpromazine treatment. This leads one to suspect that the spider has difficulties in starting its web-building comparable to those of our subject when he wanted to start his morning shave. If web-building was once begun, however, the whole subtle sequence of movements ran off practically undisturbed.

If any single one of these experiments has not convinced us that tranquilizers and barbiturates affect behavior in different ways, the parallel results of all three procedures should be regarded as strong evidence that there is a fundamental difference between the ways that the two drugs affect behavior. One, the tranquilizer, inhibits drive, possibly initiative, the ability to start something, while the other, the sleeping drug, in a sufficiently high dose, interferes with the execution of the act itself—whether this is rope-climbing, spontaneous activity, or web-building.

Attacking it from another angle and arriving at similar results qualitative rather than quantitative differences between barbiturate and tranquilizer effects were established experimentally and measurably by E. and K. Killam (1956, 1960). These investigators used unanesthetized cats which had chronically implanted electrodes in their brains. Two pairs of bipolar stimulating electrodes lay in the diffuse thalamic projection system, one in the nucleus centre median or nucleus centralis lateralis and one in the reticular formation at the level of the mesencephalon. Bipolar recording electrodes were implanted on the surface of the cat's brain. For a stabilization period of two months no drug experiments were made. Every day the animals were put into an observation chamber and watched until they went to sleep. The experimenters made sure that their animals slept by establishing criteria for sleep like: sleeping position, closed eyes, respiration regular and deep, and the characteristic synchronized sleeping EEG. Then, one of the two systems, the reticular formation or the diffuse thalamic projection system, was stimulated at one minute intervals with increasing voltage until arousal was obtained. In this way the threshold voltage for each system was determined. Arousal was defined in two ways: 1) an EEG desynchronization which outlasted stimulation, so that they knew that desynchronization was propagated and did not depend on the stimulus voltage. 2) The behavior similar to normal awakening defined by yawning, stretching, scratching, looking around "non-attentively". Such a response was assumed to be specific for arousal also because higher voltage caused a totally different behavior pattern. This can be described as "startle response".

When drugs were given, certain changes in the threshold for arousal stimulation could be measured. Reserpine 100 microgram/kg (corresponding to a human dose of about 5–10 mg/person) did not change the threshold. Chlorpromazine after 5 mg/kg (corresponding to about 250–500 mg/person) sometimes showed a slight elevation of the threshold of about 20%, and arousal was slower. Pentobarbital was chosen in a non-anesthetized or non-neurotoxic dose of 5–10 mg/kg (corresponding to 0.5–1 g/person). It elevated the arousal threshold always more than 100% and frequently more than 200%. The authors concluded from these and similar experiments that chlorpromazine and reserpine did not alter the reticular formation, where their stimulating

electrodes lay, in such a way that arousal was not possible. Pentobarbital, in contrast, causes a true depression of transmission in the reticular formation.

Keeping in mind the important role which the reticular formation plays in the waking brain (H. W. Magoun, 1958) these results lead us to have a deeper understanding of tranquilizer effects as opposed to those of barbiturates. I would like to quote verbatim some of the Killams' conclusions from these experiments because they are part of the foundations of our present-day concept of the tranquilizers' mechanism of action. "First, neither chlorpromazine nor reserpine directly alters the reticular formation so that the fundamental processes involved in the phenomenon of the "arousal" are non-functional. Second, chlorpromazine appears to augment rather than depress the neural mechanisms for the representation of the peripheral events in the reticular formation. Third, chlorpromazine also appears to enhance the inhibitory downstream effects of the reticular formation on afferent input. This alteration may be one mechanism by which chlorpromazine modifies behavior. Fourth, reserpine seems to alter some fundamental processes as yet ill-defined, controlling the organization of behavior." The authors note that, "in contrast to chlorpromazine, pentobarbital at 10 mg/kg decreased the the afferent-evoked potentials in the reticular formation . . . Conduction within the reticular formation was similarly depressed . . . The chlorpromazine induced depression in the recovery cycle of the reticular formation (established by measurements of recovery cycles in the same preparation) is qualitatively different from that induced by barbiturates."

Up to this point I have tried to bring evidence from animal experimentation to show that tranquilizers are fundamentally different from the older central depressants. This does not only relate to therapeutic range or dose, but the point of attack in the brain and the mode of action of tranquilizers can be distinguished from that of barbiturates and other sedative drugs. Let us now shift the approach and ask another question: Can animal experiments tell us also something about possible beneficial effects of tranquilizers which have not yet found application in medicine? I want to report on results of a group of recent experiments with animals using tranquilizers by S. Mallov and P. N. Witt (1961). They seem to have some bearing on human medicine. In this series barbiturates have not yet been tried so that we are unable to tell whether they would act similarly.

The experiments were performed with rats in plastic cages with a metal grid floor. Electric shocks of low AC voltage were applied at irregular intervals through the grid. No escape from the shocks was possible. In observing the animals it seemed that they built up increasing tension, anticipation and fright. Though voltage was in the course of the procedure sometimes even decreased, the animals jumped, squeaked, urinated and defecated more and more. Between shocks they sat in the corner of their cage with arched backs, hair on end and tails raised. After 0.5, 2, 4 and 7 hours the rats were sacrificed and the blood withdrawn. The free fatty acid level in the plasma was determined by the methods of Dole (1956) or Schotz et al. (1959). A difference between the shocked and control rats became soon apparent. After only 2 hours the shocked rats showed a significant rise of 32% in free fatty acids over unshocked controls. This rose after 4 and 7 hours to 51 and 126% respectively. There seems some similarity to observations on humans. Here a correlation between periods of stress, sustained drive, conflict, anxiety, anger, hostility and high serum cholesterol or high non-esterified fatty acids could be established (M. Friedman, R. H. Rosenman, 1959; J. F. Hammarsten et al., 1957; M. D. Bogdonoff et al., 1959). Such observations have formed the basis for the proposed mechanism of stress inducing through a rise in blood lipid concentrations a tendency for lipids to deposit in arterial walls. Our experiments on rats seem to be useful models because these animals have been shown to have considerably more coronary atherosclerosis after 10 months

on a high fat diet and being exposed to repeated anxiety (H. N. Uhley, M. Friedman, 1959).

In further experiments 9 rats received 4 mg/kg chlorpromazine subcutaneously 5 minutes before stressing was begun. After 4 hours these animals showed lower free fatty acid levels than those stressed without drug. They also appeared more quiet and relaxed. 8 mg/kg chlorpromazine given 5 minutes before stressing lowered free fatty acid levels even more. And if the drug was given 1 hour before stressing was begun, no increase in plasma free fatty acid levels above controls could be found. These latter animals had hardly reacted at all to the electric shocks, had shown no excessive urination and defecation, and had appeared to the observer much less tense. They were, however, not unconscious or anesthetized. They seemed to feel the shocks but react less to them.

Chlorpromazine is known to possess antiadrenergic properties in addition to its central nervous system effects. Epinephrine is a likely mediator for the increased output of free fatty acids under stress. Consequently these experiments were no basis for distinguishing between a central and an adrenergic blocking effect of the drug. In order to ascertain that the central tranquilizer effect is responsible for the prevention of a rise in the free fatty acid levels a second tranquilizer was tried. Meprobamate (Miltown) has supposedly no effect on the autonomous nervous system. When 200 mg/kg were administered as a 4% suspension in a 5% solution of gum ghatti by stomach tube one hour prior to stressing to our rats, a similar relaxation in behavior and no rise in free fatty acid levels was observed. It could also be shown that each drug administered alone to unstressed rats showed no effect on free fatty acid levels. From this it can be concluded that it is possible to inhibit the free fatty acid response of rats to stress by tranquilizers through their effect on the central nervous system. Whether similar effects on humans can be shown with therapeutic doses is an open question. But the animal experiment makes it worthwhile to spend time and effort on clinical tests.

Let us try to sum up what information these and other experiments have given us about tranquilizers. This group of drugs which comprises chlorpromazine (Thorazine), reserpine (Serpasil), meprobamate (Miltown) and several more has properties as well as an area of attack in the brain which distinguishes it qualitatively from sedatives and other centrally depressant drugs. Through their ability to diminish drive, decrease anticipatory fear and anxiety without initial excitation they may become useful in preventing physical consequences of stressful events. They have side-effects outside the central nervous system and can cause undesirable reactions which should make the physician discriminating in their use. Only when their expected beneficial effects outweigh their danger should they be prescribed. The knowledge of what tranquilizers can and cannot do, which is based on experimental evidence, will help us to pass from the period of doubt in their usefulness (which followed their enthusiastic and indiscriminate acceptance) into an era of rational therapeutic use. I am certain that there will be many patients who will profit from the specific effects of tranquilizers and who cannot be helped by any other drug.

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