General Discussion

Dr. Daly: We are indeed indebted to Dr. Wada for organizing this stimulating, if I may use that word, conference. In asking me for comments, he is essentially consulting the opinion of the "man in the street", since I have no immediate experience in this area. Nevertheless, one cannot consider this fascinating model of epilepsy without immediately perceiving a number of questions that deserve further exploration. In this context, let me speak briefly about three areas.

The first concerns the relationship of kindling and memory. The word "memory" is a deceptively simple term which implies underlying units for what is in reality a diversity of processes and mechanisms. For example, chromosomes supply, through the DNA-RNA mechanism, long-term, as-it-were, racial memory, which may result in largely unmodifiable, morphologically distinct patterns of neuro-organization. I refer specifically to the asymmetries of structure in the primary and secondary auditory areas of the two cerebral hemispheres in man. This asymmetry, first noted in adults (Geschwind and Livitsky, 1968), has subsequently been shown to be present at birth (Wada 1969, Witelson and Pallie, 1973) and makes it appearance by the 29th week of gestation (Wada, Clarke and Hamm, 1975). In ordinary circumstances, this asymmetry of structure presumably reflects the asymmetry of function of the two hemispheres in language and speech.

In contrast, the term "plasticity" refers to enduring modifications in neuronal connectivity in response to environmental stimuli (Horn, Rose and Bateson, 1973). Such modifications in connectivity develop particularly during the so-called critical period of maturation in the nervous system. Thus, Hirsch and Spinelli (1971) have shown that if newborn kittens are deprived of normal visual experiences and exposed only to visual environment of either horizontal or vertical lines, then the striate visual cortex will contain predominantly simple cells, selective for the orientation seen, and will lack units sensitive to orthogonal orientations. Such plastic alterations are reflected in behavioral changes observed in kittens raised in visual environments lacking certain contours (Muir and Mitchell, 1973). One may ask if kindling operates even more powerfully in a maturing brain. Will the establishment of the process be accelerated if initiated before the animal reaches maturity? It appears that afterdischarge is essential to the establishment of kindling. Does this mean that kindling cannot be demonstrated in a brain too immature to exhibit afterdischarge?

If kindling somehow "teaches" the brain to become spontaneously epileptic and, in this sense, the brain "remembers" to be epileptic, can the brain also forget to be epileptic? What will be the ultimate fate of those animals which have developed spontaneous seizures if further stimulation is omitted? We know that in human epilepsy spontaneous remission may occur, often with relatively great frequency, for example in "absence" epilepsy and post-traumatic epilepsy; but by what mechanism? Can this process be compared in any way to forgetting, or is the latter a failure of recall rather than retention? If spontaneous seizures can be induced by kindling in the immature brain, will these be more enduring, as a result of plasticity, than those initiated by kindling in the mature animal? Clearly, a host of questions about the natural history of human epilepsy may be illuminated by such use of the kindling model.

A second area of interest which appears unexplored as yet is the relationship of sleep and epilepsy. Sleep influences epilepsy and epilepsy influences sleep, although in the human being these influences are still not well understood or, indeed, even adequately described (Daly, 1973). The reports that we have heard earlier from Drs. Sato and Tanaka indicate that this can be a profitable direction for study. For example, if the basic rest-activity cycle (BRAC) of Kleitman does indeed modulate the circadian distribution of seizures, will this modify the kindling process? In other words, will kindling be differentially affected if stimulation is carried out in the waking or sleeping states. Further, if such a differential effect exists, would kindling be more effective if carried out in REM or NREM sleep? Blocking norepinephrine synthesis modifies the seizure threshold (Corcoran et al, 1974). Does this operate via the noradrenergic system of the locus coeruleus which modulates REM SLEEP (Jouvet, 1972)? Alternatively, one might question what the effect would be of blocking serotoninergic mechanisms of sleep with parachlorphenylalanine. Finally, one might ask what role dopaminergic pathways might exert on kindling since alpha-methylparatyrosine exerts such a dramatic action in blocking established morphine addiction in the monkey.

Thirdly, an area which has not been explored at this conference concerns the influence of hormones on seizure mechanisms. In human epilepsy Laidlaw (1956) has studied the relationship between menstrual cycles and seizures. Seizure risk decreases in mid-cycle co-incident with progesterone release during the luteal phase. Conversely, an exacerbation of seizures occurs at the onset of bleeding, perhaps as a result of estrogen release. Furthermore, pregnancy far more often exacerbates than ameliorates epilepsy (Knight and Rhind, 1975), perhaps as a result of rise in estrogen levels. In animals, application of estrogen to the cortex in the region of an experimental epileptogenic focus results in an increased rate of firing (Logothetis and Harner, 1960). This is an old story to Dr. Morrell, who showed that administration of estrogen to women with catamenial epilepsy "activated" EEG abnormalities (Logothetis et al, 1959). Parenthetically, Dr. Morrell promised us an answer about the clinical effects of estrogen on seizures but, to my knowledge, has never published further on this.

Does this relate to kindling? I asked yesterday if there was any difference in kindling in male and female rats and was told that in the female rat kindling is much more unpredictable and inconstant. Perhaps this relates to the time in the oestrus cycle at which kindling is carried out. Whether androgenic hormones would exert any analogous influence remains a purely speculative consideration. In any event, clearly, the exploration of hormonal influences on kindling could yield much valuable information.

One final observation deserves comment. Dr. Adamec's data suggest that even the kind of minor electrical stimulation involved in kindling can modify behavior. This has serious social implications in terms of contemporary concerns about behavior modification through psychosurgical techniques. If it appeared possible to modify behavior by kindling, this might expand again the arena of debate about the legitimacy of experiments on behaviour modification in human beings (Goldstein, 1974).

Let me reiterate that we are all indebted to Dr. Wada for organizing this enjoyable and productive meeting. I am grateful for having been included.

Dr Wada: Thank you, David. I would like to now ask Dr. Stevens for her comments.

Dr. Stevens: This symposium with its rich bill of fare has acquainted me with many new concepts which are provocative for the clinic as well as the laboratory. The distinct differences between kindling in the limbic system and neocortical sites are evidently accompanied by fewer savings in transfer of excitability, and tend to support the schizophysiology so near to the heart of my first teacher and collaborator, Paul MacLean. The once daily stimulation thought to be necessary early in the kindling days of Goddard and Morrell has apparently been modified progressively downward until now the limits seem less to be set by time than by the elicitation of afterdischarge. If this is true, what does it portend for the protein building memory process proposed by Morrell? The question posed by David Daly seems crucial here — does the cycloheximide also inhibit kindling after it is full developed — it should not do so if the protein synthesis hypothesis is to be sus-

tained. Why is it that rats on ICSS or MFB rarely become chronically epileptic? For those of us interested in kindling as a model of epilepsy or other disorders in which altered system excitability plays a role in human pathology, the propagation pathways for spread of the kindled focus is of crucial interest. The epileptic focus concept is replaced by the concept of an epileptic system, as recently very elegantly developed by Stepanova and colleagues from Leningrad, who pointed out the crucial role of breaking through the barrier of the caudate nucleus appears to play in the spread of seizure activity from a temporal lobe amygdala focus in man. Indeed, Goddard tells us that stimulation of fiber systems is even more effective in kindling seizures than stimulation of the primary nuclei from whence the axons arise. Is it possible then that generalized seizures in a child which kindle the greater excitability within the limbic system are related to the very different striatal projections for most of the limbic structures compared with those of neocortex. The entire neocortex projects topographically on the caudate-putamen; in contrast, the hippocampus, amygdala and pyriform cortex project to islands of tissue whose histofluorescent properties and ultrastructure are altogether similar to neostriatum but which are located anterior to the head of the caudate nucleus in nuc. accumbens, nuc. stria terminalis and diagonal band, olfactory tubercle. Moreover, the dopamine terminals on the interneurons of this limbic striatum originate from the ventral tegmental area of Tsai and not from substantia nigra. Recent evidence suggests that the regulation of DA and acetylcholine in limbic striatum has significant differences from neostriatum. GABA concentration is also greater in accumbens than in neostriatum. For those of us interested in kindling as a model of epilepsy, it is crucial to determine at which point in the propagation pathway, interruption is most efficacious and least damaging to the overall function of the organism. As I noted yesterday, the Russians have recently reported some early success with repeated focal stimulation of pretested effective sites in caudate nucleus for the treatment of epilepsy. This may in itself constitute a form of kindling of an inhibitory pathway. To replace the brutal application of generalized convulsions in man with discrete stimulation of significant regions for the control of depressive and schizophrenic psychoses would constitute a major breakthrough in drugs and is presently under study in Czechoslovakia and the U.S.S.R.

The evidence that catecholamine and GABA systems are affected by the kindling procedure suggest one route by which repeated generalized convulsions given as treatment in psychiatric disorders may affect behavior. Adamec's investigation of the behavioral and remote electrophysiologic consequences of kindling in cats is of particular importance as is the need to stop considering the amygdala as a homogeneous area from which similar responses are to be expected from all quadrants. The effects of sleep, ontogenetic changes and gonadal steroids in facilitating or inhibiting kindling may relate to the clinical problems of obsessions and other psychopathologies which seem to arise from overuse of well worn thought pathways.

My own interest in kindling was kindled by Goddard and Morrell as we walked along Riverside Drive in New York four or five years ago and consolidated in my reward system by our attending a superb performance of Tosca that evening at the Lincoln Center. Recently, kindling has come into practical use in our laboratory as we attempt to build a schizophrenic cat. Impressed with the similarity of clinical phenomeology of schizophrenia to discrete aspects of the aura or automatisms of temporal lobe epilepsy and with the DA hypothesis of schizophrenia which emerged from the efficacy of DA blocking agents in that disorder, led to the hypothesis of possible DA hypersensitivity in the superior terminals of the mesolimbic DA system in limbic striatam. DA release in nigrastriatal system is modulated by feedback loop from striatum to nigral DA cell, which is GABA coded at the nigra. I wonder if similar regulation by GABA feedback obtained for VTA leads to remarkable behavior changes and spike activation in nuc. accumbens of freely moving cats. These changes endure 15 to 20 minutes and are enhanced by CA agonists and blocked by haloperidol or pre-application of 6-OHDA. We now are attempting to kindle this region in intact cats and in those treated locally with 6-OHDA. Daily stimulation for 2 sec with biphasic 1 ms pulses at frequency of 80-100 cps with currents of 200-800 ua induces a brief behavior response but no afterdischarge has been recorded. Progressive behavioral changes, similar to those which acutely follow bicuculline have been induced in a chronic stimulation which has had a previous local bicuculline induced generalized convulsion. The associated EEG changes also resemble those of our bicuculline treated cats. Sleep EEG's reveal important changes in activity at the stimulation site and in remote electrodes subcortically.

Dr. Wada: Thank you, Jan. I would now like to ask Dr. Fernandez-Guardiola for his comments.

Dr. Fernandez-Guardiola: The kindling process leads to a facilitation of convulsive activity. This facilitation is proved by the fact that stimuli of less intensity are progressively needed to elicit an afterdischarge and a seizure. That undoubtedly means that there is a lowering of theshold in the stimulated site of the brain.

A problem arises related with the nature of the "spontaneous" seizure that appears at the end of the kindling process. It seems to me that sensory precipitation of this "spontaneous" generalized seizure cannot be discarded. It is true that this seizure appears without any manoeuver effected by the investigator. It is also true that environmental or internal propioceptive stimuli are freely reaching the kindled areas of the brain. This would remind us of the classical reflex epilepsy which was described early in this century by Amantea (1912), Clementi (1929) and Baglioni and Amantea (1914). These authors proved that the increased excitability in the primary sensory cortical projection areas provoked by subthreshold amounts of strychnine was sufficient to make an animal respond with a seizure when sensory stimulus otherwise normal in its intensity was applied. This experimental model of epilepsy was useful for the understanding of some types of human epilepsy that could be classified as sensory epilepsy. Nevertheless, there are some notorious differences between kindling and this animal model of reflex epilepsy described by Amantea, Baglioni and Clementi. Sensory epilepsy provoked by strychinization of the cortical area proved to be very specific for one determined sensory modality, while kindling as we saw, particularly in Pinel's presentation, is a general phenomenon probably a non-specific sensory process. Another noticeable difference is the long term stimulation necessary to elicit kindling and also the weakness of this stimulation.

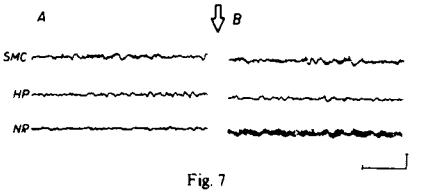

Fig. 7

Subthreshold stimulation of the sensori-motor cortex (SMC). *A*, control; *B*, appearance of the fast sinusoidal activity in the red nucleus (NR). HP: dorsal hippocampus. The arrow marks the cortical stimulation. Calibration: 1 sec, 100 μV.

Taken from: Fernández-Guardiola, A. and Ayala, F. Red nucleus fast activity and signs of paradoxical sleep appearing during the extinction of experimental seizures. Electroenceph. clin. Neurophysiol., 1971, 30: 547-555.

Figure 2.

Most of the works presented in this Symposium have dealt with the excitatory aspect of kindling. There is no doubt that from the beginning of the stimulation provoking the kindling process the brain inhibitory structures must react against the progressive activation of the kindled structures.

The subthreshold weak stimulation of the motor cortex provokes, from the beginning, notorious acceleration and changes in morphology of the red nucleus electrical activity even before the appearance of any cortical electrical modification (Fernandez-Guardiola et al., 1971) (Fig. 2). This fast subcortical activity is recorded not only in the red nucleus but also in the bulbar olive and in the Purkinje cell layer of the cerebellum and is concomitant with a strong monosynaptic reflex inhibition in the spinal cord (Ferandez-Guardiola, Munoz and Velasco, 1964).

One promissory research line in the future would be a study on the changes in activity in the caudal structures of the brain during kindling development. It is a remarkable fact that these structures, especially the red nucleus and cerebellum, did not kindle, as was shown by Goddard in the opening paper of this Symposium.

The difference between the frontal and amygdala kindling described in the elegant experiments by Wada's group could also be explained on the basis of differential action of the subcortical inhibitory structures upon the rostral portion of the brain.

A number of epileptic patients have been

implanted with electrodes in the cerebellum in order to control the seizures (Cooper et al., 1974). Some of these patients have been daily stimulated for periods of 8 min ON/8 min OFF with electrical currents. The EEG recording of such patients did not show any spiking activity that could be attributed to the cerebellar stimulation; on the contrary, the interictal spiking activity of temporal lobe epilepsy seems to be depressed by cerebellar stimulation. Moreover, this procedure of chronic cerebellar stimulation seems to improve sleep in a group of these patients (Contreras, Cooper, Fernandez-Guardiona, 1974).

Dr. Wada: Thank you, Augusto. Now it is open to all participants. Yes Dr. Burnham.

Dr. Burnham: I would like to respond to Dr. Stevens. I was going to hide these data and give them to you later. They are not fully analyzed yet. She asked about transfer between the cortex and the limbic system. We have some studies on this that we are still working on. I think that I would say that yes, it does occur or at least we think that it occurs, but we have to go back a little bit. It is not easy to explain. I think that what we will have to recognize from now on is that our terminology originally was cortical seizures or subcortical seizures. I think that we are going to have to change our terminology to say generalized seizures triggered from the limbic system and generalized seizures triggered from the cortex. Originally, when we stimulated the cortex we saw only very brief seizures which didn't really look quite like the seizures that we triggered from the limbic system but we said fine, that's the way the cortical seizures look. Since then, it has become clear that if you space your stimulations properly the cortex will also drive the kind of long lasting, clonic generalized seizures that you usually trigger from the limbic system. Essentially, we have local cortical seizures which happen to produce motor seizures because you are in a motor area. You have local limbic seizures, which we don't talk about too much, and then you have generalized seizures driven either from the limbic system or the cortex. This long prologue is also what is transfer? Generally we talk about transfer in terms of how many afterdischarges it takes to produce a grand mal generalized seizure. Thinking about it from that point of view, we have triggered seizures from the cortex and then later looked to see if the amygdala was potentiated. There was a trend towards this but it was not significant on most of the different measures. I think however, that we had not triggered enough cortical seizures. I triggered 10 seizures, but not 10 generalized cortical seizures — they were local seizures. It was not reactive propagation or much to speak of in the limbic system by the time the animal had had those 10 local seizures triggered from roughly areas 4 and 6 in the rat. I don't think that we have really given a good test of the spread of transfer between the cortex and the amygdala but are in the process of doing this. Does triggering seizures in the amygdala make it easier to trigger seizures in the cortex? We have to look at this in two ways. (1) Local cortical seizure facilitating other local cortical seizures. As far as I know, we don't see this in the limbic system but Ron has shown it in the cortex in several different ways. (2) Look at how long it takes the cortex to trigger grand mal convulsions. In this case, when you previously trigger seizures from the amygdala it is pretty clear that the cortex will trigger them sooner.

Dr. Racine: Dr. Morrell raised the question about the appearance of inter-ictal spiking in rats. Actually, we see it in most of the hooded rats that we test, and it appears to be similar to the spiking reported by Dr. Morrell for the frog and Dr. Wada for the cat and baboon, although the density is usually less than in those species. Dr. Stevens questioned the role of protein synthesis, as studied by Dr. Morrell, in the kindling effect in view of her understanding that kindling will occur with very short intertrial intervals as long as afterdischarges are triggered. Dr. Goddard has demonstrated an inter-stimulation interval effect on kindling and we have studied it in more detail. With stimulations separated by 15 minutes, kindling will progress normally for the first 4-5 discharges. If separated by 30 minutes kindling progresses normally for the first 8-9 discharges, and at one hour intervals we found no significant differences compared to animals stimulated once every 24 hours. These changes are still pretty rapid but it is possible that, like short term and long term memory or the transient and permanent phases of post-tetanic potentiation, the changes during "massed" kindling stimulations may have a different mechanism than that underlying the permanent changes that result from those stimulations.

Dr. Livingston: I would like to make just a couple of general comments because I think that this meeting is historically significant. It marks the first real focus from a rather broad perspective on this problem of kindling. If you look back on the program, I think that it was arranged in a very fortuitous way, starting off with Graham Goddard's serendipitous exploration so beautifully carried out of this problem which was originally a contaminant of his study, and Graham emphasized that he really was not interested in the seizure parallel with epilepsy problem but in the potential models that this might present for learning and memory. Then, the final paper of Dr. Adamec's in which you have now come through this whole cycle in which there is a lot of epileptic discussion in between to the behavior component of this. I think that the effect this discussion may have in the future is it will mark the bridging of the great gap that has existed between physiology, neurology and psychiatry which should have been bridged years ago by what we know and documented about temporal lobe epilepsy. The changes that occur in psyche and behavior in temporal lobe epilepsy should have provided the link to understanding the physiological basis of psychiatry that was, unfortunately, missed. However, I think that in the exploration of kindling, the fact that was pointed out here, too, was that the stress which we measure and which we find so nice to work with, electrical stress by which we induce kindling, now can be regarded in general terms as altering the response and the threshold behavior of the brain as a whole to many other kinds of stress. I think that this gives us the mechanism for shifting from the physiology that we define so easily to the physiology that must be there but which we don't define so easily in terms of emotion and behavior. I think that this conference is going to have a very significant place historically in that evolution.

Dr. Pinel: I was very interested in Dr. Daly's comment about the possible interaction of hormones in kindling because a study was recently completed in our lab by two students, Ron Mucha and Gercharn Dionne, working with Tony Phillips and myself, in which we looked at the effects of fluctuations in estrogen levels on kindling. Our initial finding was what Dr. McIntyre commented on earlier, in that we noted that the females were tremendously variable. When you looked at the means and compared females and males there was very little difference but when you looked at the variability there was tremendous variability in the female scores and not in the male score. We then began taking vaginal smears and found that this variability could be correlated with the menstrual cycle. During the estrogen surges we found that the duration of seizures was much greater. In a subsequent study we ovariectomized females and found that this eliminated the variability and they in fact behaved in much the same manner as the male animals.

Dr. Burnham: Can you absolutely rule out that there is any electricity which could get through the electrodes? I found this to happen from sitting on a plastic chair while I was kindling amygdala in rats. After a while, the threshold dropped so low that I picked them up to plug them in and they would go off in my hands from static electricity. After you have been stimulating for six months or so, the thresholds must be tremendously low.

Dr. Pinel: Stimulation does not necessarily reduce afterdischarge thresholds. In fact, the levels we used increased thresholds. I can confirm your observations in that at times, we had some very tricky problems although not with the spontaneous series. We thought we had seizures that were conditioned to the apparatus and we were never able to measure ourselves or find anybody that could measure these currents that were being generated in our leads. We knew they were there because they would not occur when we disconnected the lead or put a string dummy on. We see spontaneous seizures when the animals are in their home cages or not anywhere near any electrical equipment.

Dr. McIntyre: I have seen animals bump against the side of the cage and have a seizure.

Dr. Morrell: This is possibly what Dr. Fernandez-Guardiola was talking about. You don't know if you have an electrical event. It may be a large focal potential or a large sensory event that sets off the seizure. I would like to raise the possibility that there is some

relationship between the kindled area and what Rusinov of the Soviet Union has called dominant focus. Nobody knows what dominant focus is and I do not know if this is useful to raise, but I raise it because one feature of such an area defined in that way was its successive response to sensory stimulation. Graham, can you kindle the optic nerve?

Dr. Goddard: No. I have stimulated the optic tract, also at the level of the commissure, where you can be absolutely sure that is all you are stimulating. I carried these animals for 200 days and have not seen any seizure or convulsions. The white matter is very good because both Racine and myself have had a fair amount of experience with anterior commissure, corpus callosum, and especially with hippocampal commissure. I have had some experience with fornix and stria terminalis which is very difficult to deal with because it is hard to get an electrode in either of those and be sure that you are not also stimulating cells adjacently. You are better off in the hippocampus because you have a fairly large area to deal with.

Dr. Morrell: Do you think you could be stimulating both areas? Do you think that antidromic activation may be important?

Dr. Goddard: I think that antidromic activation may be important in kindling. I have just completed or just written but not completed, a study from kindling in the hypothalamus. The one thing that seems to be the simplest interpretation of the results is that the hypothalamus has extremely high thresholds and you can kindle convulsions from the hypothalamus but if you do I don't think that you are really doing it in the hypothalamus. Rather, what you are doing is kindling some other structure by possibly antidromic activation, but that there is also orthodromic activation. This is a testable kind of thing but also extremely difficult because when you cut the terminals of a tract, you have to maintain the tract and avoid sprouting so that technically I do not know if that question is going to be answered unequivocally but I would certainly accept the likelihood. You then have to ask the question if this acts on collaterals somewhere further back towards the cell and is it still orthodromic?

Dr. Morrell: Could you comment on Dr. Steven's question about the intracranial self-stimulation studies and also any thoughts on brain stimulation in man.

Dr. Goddard: When I talk about self-stimulation studies, I'm talking about rats and cats but mostly rats where most of the work has been done, and not including goldfish. When I first got into this kindling the very first thing that I tried to do was to say, why don't all these self stimulators see this? So, upon looking at their literature, as you read the fine print, you will see that they all see it. If you talk to them, they say sure, they see that all the time. That's just because the electrode has been in the brain too long and what we do is work with our animals for a while and if epilepsy develops we chalk them off and get some fresh animals. Areas differ, but if you can trigger an afterdischarge somewhere in the brain from blasting a hypothalamus it kindles as rapidly as amygdala. One of the quickest checks that you can make on the literature for this effect is whether or not they say that the animals satiate with certain types of reward. They say that you never satiate, for the hypothalamus. An animal will press for 48 hours until he drops from exhaustion, whereas the septal area satiates very rapidly. He will press for it for a little while and then he will have had enough and want to press again. In other words it is not satiation as such but probably a post-ictal refractoriness. I would be amazed if kindling doesn't occur in man.

Dr. Phillips: I would like to add to some of the comments that Dr. Goddard was making with regard to self-stimulation. Dr. Stevens and I had the pleasure of attending a marvelous conference in Beerse, Belgium a couple of weeks ago on intracranial self-stimulation. It is not often that you get the pleasure of attending two excellent meetings in the same month. I would briefly like to review some of the points dealt with at that meeting which may have some bearing on the kindling phenomenon.

One of the main themes of the brain stimulation conference was the role of the catecholamines in brain stimulation reward and I was pleased to hear an emphasis on the role of the catecholamines as possible inhibitors of seizure activity in the epileptic state. In reviewing the relationship between self-stimulation and kindled epilepsy, self-stimulation sites at which brain stimulation reward is not confounded with seizures, are sites that either contain cell bodies of catecholamine systems or their axonal projections. These would include structures such as the locus coeruleus, substantia nigra, and the mesolimbic system. High rates of self-stimulation are observed at these sites, yet I have never seen seizures from these structures. The picture changes completely when you move into those areas of the brain to which the catecholamine systems project. Here I'm thinking of the nucleus accumbens, the septum, the caudate, putamen, olfactory bulb, amygdala, cingulate cortex and the frontal cortex. All of these structures have been related to kindling at this meeting and each is postsynaptic to catecholamine systems. Therefore, it is possible that kindled seizures result from the artificial activation of systems normally inhibited by the ascending catecholamine projections.

In support of this admittedly speculative hypothesis, let me describe the results of a recent experiment on self-stimulation in the caudate-putamen (Fibiger, Carter and Phillips, 1975). The purpose of the study was to show that self-stimulation in the caudate is dependent upon dopamine innervation. The experimental design called for a unilateral removal of dopamine innervation of the caudate with 6-hydroxy-dopamine. Subsequently we saw an abolition of the self-stimulation in the ipsilateral caudate-putamen. However, the seizures which often accompanied self-stimulation prior to the lesion were potentiated. In the pre-lesion state we would perhaps only see one seizure but in the post-lesion stage we would often see several intense seizures. Given the observation, it will be very important to examine the effects of selective lesions of catecholamine systems on the development of kindled seizures and the magnitude of well established seizures.

Dr. Goddard: One of the things that I tried to do ever since I started this thing and did the mapping study, was to try to think of a single notion that would gather together all the positive sites for kindling and distinguish them from all those areas that do not. I have had a lot of thoughts about it but nothing has ever been consistent. I have never had a single good idea that would put it all together in one simple, elegant statement and I would like to congratulate Tony Phillips. It may be the wrong idea but it is the first clean, simple statement that has ever made any sense to me.

Dr. Wada: We have been engaged in a prophylactic study in kindling cat preparations and are now extending it to *Papio papio*. I would like to ask Dr. Cain to briefly comment on his observation in this area.

Dr. Cain: Based on some promising prophylactic effects of a number of anti-epileptic drugs in the amygdaloid kinding cat preparation obtained in this laboratory, we have begun a study designed to assess the prophylactic efficacy of these drugs in the amygdaloid kindling baboon (*Papio papio*). Carbamazepine appears to provide a very effective supression of seizure development and nearly complete suppression of afterdischarge, with very few toxic symptoms. Phenobarbital also effectively suppresses seizure development and afterdischarge, as evidenced by the animals remaining in Stage 1 or 0 after 72 daily stimulations when they would normally have progressed to the final generalized bisymmetrical seizure Stage 5. However, in these animals there are some toxic symptoms. Results from the ongoing re-kindling phase of the experiment, without the drug, indicate normal seizure development, and thus a genuine prophylactic effect.

Dr. Burnham: Since the question of taurine has come up, we might add our results in a little more detail. We've worked in rats, with Van Gelder's advice. We have also been unable to find any effect of taurine. We have not looked at the subtle things but we have done subcutaneous injections as well as cannulating it directly into ventricles. We have used kindled animals and we have used animals which we have kindled in the course of the experiment. We have also used cortical and subcortical placements. I think that the fact this drug appears to work well on some types of seizures and does not appear to work on kindling might be a very interesting finding in something that would tell us how the drug works.

Dr. Livingston: I want to reinforce what Dr. Pinel said and also to comment on what Dr. Ojemann may be going to say. In relation to what Dr. Wada was speaking about, that is,

Dilantin being very effective in suppressing a frontal cortical focus, we found that Dilantin was very effective in blocking cortical seizure development whereas it actually facilitated, very strikingly, the development of seizures with amygdala kindling. There is a lot of clinical evidence that fits this association and similarly Procaine does essentially the same thing. That is, Procaine is remarkably effective in blocking seizure excitation from cortical stimulation but is actually a stimulant and facilitates development of seizures from amygdala stimulation. Valium, on the other hand, has remarkable suppression of limbic amygdala kindling and there is relatively little effect on cortical excitability.

Dr. Ojemann: I would like to make three comments. The first is about the prophylatic study which Dr. Richard Rapport and I have done. It will appear in the Archives of Neurology. We used an epidural cobalt model as a model of seizures developing from a cortical injury. Adult cats with cobalt over the sensorimotor cortex developed electrographic signs with an occasional spontaneous seizure that developed over a period of about 10 days and persisted for 10 weeks or so, in the untreated animal. If you give these animals diphenylhydantoin for a period of 1 month, at which time the control animals are still quite hot, the treated animals do not show either the electrographic or spontaneous seizures. Nor, in fact, do they show the changes concerning potassium, AD, TPA's which appear in the animals with spontaneous seizures. So it is pretty clear in this model that diphenylhydantoin has a prophylactic effect, that if you give it for a period of time the seizure focus simply does not develop. Interestingly enough, it does start to develop. It develops over a period of about 5-7 days and then it stops and the question that I would direct to those studying kindling is whether you can identify a sort of critical period, relatively early, where the process may suddenly become irreversible and go on to developing spontaneous seizures which is sort of what our data looks like. For those of you studying taurine let me give you some data that may make you more comfortable. As you know there is at least one published report that taurine is diminished in human epileptic foci. We have been measuring this and now have data from biopsy samples on, I think, 2 human foci and, in our measurements at least, the taurine levels are completely normal.

Dr. Wada: We have done similar observations with human epileptogenic foci which will appear shortly in the Archives of Neurology. Dr. Perry's amino acid analysis on 9 patients' removed foci, defined electrocorticographically, failed to show any decrease of taurine but did show an increase of glycine in some patients. I think the applicability of a taurine deficiency model of epilepsy is limited.

Dr. Ojemann: The third comment I would like to make, if Dr. Wada will allow me, is in regards to the hazards of brain stimulation which Dr. Pinel discussed. This is not an academic question anymore. There is an investigational approach to the study of chronic pain which involves stimulation of various thalamic structures that is pretty close to what one would expect to kindle; that is, a period of stimulation each day or thereabouts to give chronic pain relief. I think it is a very important question. The question that I would ask of those of you studying kindling would be: Is there any evidence at all that kindling can occur in either the human brain or the brain very close to the human brain? The generalization of any phenomenon involving cortex from animal studies comparing creatures on the level of a rat to creatures on the level of man is a pretty dangerous hazard. The cortex changes enormously in the way it is organized. The second thing that we have to be careful about is that we have to be very specific that we talk not about local brain stimulation but that we talk about the specific sites involved. I've learned yesterday, that it is quite clear that kindling is much related to limbic structures. It is obviously going to make an enormous difference in terms of the role that this is going to play in the development of these investigational studies that we be very specific about the sites that we are talking about. We learned yesterday that it may be that the thalamic stimulation indeed works in an entirely different way on even kindled seizures. It inhibits them and the same may be true of, say, the cerebellum.

Dr. Pisa: Given the possibility suggested by Dr. Sato yesterday that the catecholamine system is supposedly inhibitory, I wonder whether anybody has studied the prophylactic effects of drugs like amphetamine, or if you have any feeling of what the effect of these drugs might be?

Dr. Wada: Indeed, for a long time, we have been attempting to see whether DOPA or, even better, d-amphetamine would retard seizure development. Hopefully we will have some information before too long.

Dr. McIntyre: Just a couple of comments. This cat/rat business keeps coming up all the time and it is beginning to look as though there is a rather profound difference in the amygdala between the two animals. The rat may in many respects be considerably less sensitive. The sort of thing that strikes me are some of the data of Ron and Arnold, for example, showing the cholinergic nature of the kindling phenomenon and what comes to mind then is Graham's data. I think it was Grossman's data (1966) showing how terrifically sensitive the cat is to something like Carbachol, where he has seizures that are very prolonged, lasting something like six months; whereas the rat has a much higher threshold for something like that and the kinds of things that you are describing. The fact that spontanity does not come in until considerably later may be related to some issue like that. Another thing is that Dr. Leech noticed in some of the stuff that he did a few years ago that status epilepticus can be produced without going to six month intervals. You just take a rat and kindle him and then put him on a continuous stimulation regime. There seems to be a kind of a race between status epilepticus versus the total suppression of any seizure activity whatsoever. Some of the animals go into status epilepticus and others just quit having convulsions altogether.

Dr. Morrell: Dr. Ojemann actually asked most of my questions. It's just a comment on the title of my intended paper, "the Relationship between the Mirror Focus and Kindling." One of the interesting observations is that in the mirror focus preparations many years ago, it turned out that in a drug study of Dilantin and Phenobarbital, while both drugs suppressed seizures in animals with alumina cream and freeze foci, Phenobarbital and not diphenylhydantoin prevented secondary epileptogenic lesions from developing (1959, 1961). So whereas the clinical implication is that relief of clinical seizures is not really an adequate test of optimal anticonvulsant treatment, one has to look into electrographic signs as well. In the case of the animals that we studied maintainence of diphenylhydantoin alone would ultimately result in seizures developing when the animals were taken off DPH — seizures which by that time were multi-focal and therefore more severe. The question I have of Pinel and Wada or any of the people who have been doing this, related to whether or not anybody has noticed the development of tolerance to Tegretol, Valium, (diazepam) in these studies. It seems to me that you ought to have here a very sensitive tool for picking up evidence of tolerance. For those of you who may not be aware of the clinical literature on diazepam, when that drug came out we started using it and it was incredible. Every patient stopped having seizures and mothers of children were calling us up and telling us how marvelous it was, that we had done a miracle, and this was oral Valium. Within a few months, all the seizures started to come back. Everybody then became aware that that particular drug, in terms of oral administration rapidly shows a development of tolerance and therefore very few people use it now for chronic oral medication. It should be very easy to tell that kind of information from these studies and I wonder if anyone has?

Dr. Wada: It is true that they do develop manifestations of tolerance particularly with carbamazepine in our chronic studies. If you look at the plasma levels we seem to have to increase the administration of the drug, at least in the cat, but not so much in baboons so far. In the latter the plasma level has been about 5 - 7 mcg./ml. quite steadily and effective in preventing the seizure development. With cats we have had to substantially increase the amount of our administration to maintain its prophylactic effectiveness.

Dr. Troupin: Two issues, one about Tegretol, and that is that in addition to the question of tolerance there is the question of induction of metabolism. We have studied this and seen that there is a highly reproductive latency in people's blood levels falling 3 - 5 weeks after they start taking Tegretol and this is not a progressive phenomenon because with an increase in dosage you can boost the levels back up and this does not then progressively recur.

The other issue that came across my mind as I was listening, is the fact that since the long time related events in kindling are so important in our prophylactic studies with different anticonvulsants we may very well have placed ourselves in error by matching peak time to stimulation time. It may very well be that the phenomenon that occurred between stimulation time in those 1 - 3 days depending on the animal is every bit as important as what is happening at the instant of stimulation, and that by matching the supposedly effective drug level only to stimulation time we are in fact allowing the animal model not to be protected in the significant subsequent interval.

Dr. Wada: We know repeated afterdischarge generation is essential for kindling. But we also know that a spacing of interstimulus interval is important and this implies some ongoing process between afterdischarges is similarly very important. Most of the drugs we used have a significantly high plasma level maintained during our prophylaxis study. But, as Dr. Troupin says, it may be of theoretical interest as well to see if we left afterdischarge intact but did something to the ongoing process during interstimulus interval as many experiments had been done on "memory trace" with respect to its consolidation.

Dr. McCaughran: I would like to address a comment to Dr. Goddard. This is in relation to possible amygdala activation from stimulating a site other than in the amygdala in relation to your hypothalamic work. What I did was kindle the amygdala and then start to stimulate the ipsilateral orbital cortex. I found that the current levels required were much higher than in the amygdala to evoke a seizure but transfer occurred very rapidly when current level was sufficient. What I did then in these pilot animals was to lesion out the amygdala and I found a complete blockage of seizures evoked by orbital stimulation in some of these animals. I think maybe the main problem here is that I found a recovery of seizures after a certain period of time.

Dr. Goddard: That is very nice. When I said that my study was not finished, it was because I was working with a student that quit and essentially this is what we had found. Kindling from the hypothalamus when you used these very high currents went at exactly the same rate as the amygdala. If you record afterdischarge then you invariably see the afterdischarge in the amygdala on the first occasion that it is ever triggered from the hypothalamus. Whereas if you are doing the converse, in fact, you can have an animal in convulsion without much afterdischarge showing in the hypothalamus but always when you trigger the first afterdischarge from the hypothalamus it is more prominent in the amygdala than at the site of stimulation.

Dr. McIntyre: With respect to the same thing, I take it that the nature of the activation is quite different between the two forms of stimulation.

Dr. Adamec: I would just like to amplify some of the comments of Dr. Daly with regard to the possible significance of my work seen within a therapeutic or perhaps social behavioral context. It raises very profound ethical considerations and scientific ones. In 1959, Niessen in commenting on comparative behavioral psychology has suggested that what was missing was the need for what he called axis of behavioral comparison for making cross species generalization. I do not believe even at this late date that they exist and I think that if the work I reported were to be used within a therapeutic context those axis would have to be established first; that any attempt to alter human behavior using these experimental techniques out of this kind of scientific ignorance would not only be scientific negligence but in my opinion would be criminal.

Dr. Wada: Are there any more questions or discussion? If not, then I would like to take this last opportunity to make two comments; the first one is related to chemical kindling: We already know through Goddard's study (1969) and Mason & Cooper's study (1972) that persistent alteration of behavior could follow by repeated application of chemical agents. We have also witnessed the development of recurrent spontaneous convulsive seizures in Rhesus monkeys following parental Megimide every third day at the threshold dose, which would produce spike and wave complex discharge only when intermittent photic stimulation is given. This treatment was given only for about 3 - 5 months but the animal continues to have recurrent seizures 2 years after its termination.

A couple of weeks ago, I received a telephone call from Dr. Robert Post, of the National Institute of Mental Health, who said that he was able to kindle his rats by repeated administration of Lidocaine (60 mg./kg.). He told me that his rats, so treated, showed a tendency of indiscriminate eating of feces and other usually non-edible objects. Within about 15 Lidocaine injections all his animals began to convulse. Because of the similarity of particular eating patterns to those of the familiar Kluever-Bucy syndrome and the similarity of the course of the development of convulsion, his finding is strikingly suggestive of the chemical kindling by Lidocaine through progressive functional alteration of temporal-limbic mechanisms. The unique activating property of cocaine with respect to limbic epileptogenicity had been demonstrated by Dr. Eidelberg some years ago (1963). I think that it is fair to say that a psychopharmacological approach is the mainstream of psychiatric management nowadays, using a number of extremely powerful drugs, the action of which is not yet completely understood. We know some of these agents are potentially epileptogenic, and I see from time to time, for example, tricyclic compounds producing EEG or clinical evidence of an epileptic state among psychiatric patients who are receiving them. Kindling by drugs is no longer a speculation but a reality and therefore we should be cautious and observant of what we are doing when we use potent drugs such as these.

The second point relates to our observation of baboons and Rhesus monkeys under kindling. With daily amygdala stimulation the *Papio papio* reaches the final stage within an average of about 72 days. Rhesus monkeys, on the other hand, which have been stimulated daily for the past 1 and ½ years have not gotten around to that stage yet. They are still hovering around the asymmetrical stage 4 seizure. As you know, Dr. Goddard has done some painstaking work stimulating Rhesus monkeys for about six months. Our observations so far amply confirm what Dr. Goddard found at that time. Retrospectively, one of the most remarkable differences between *Papio papio* and Rhesus monkey is that the development of focal motor seizure was extremely rapid in the former usually within about 10 - 14 days so that the initial stage of partial complex seizure is relatively short and unimpressive. On the other hand, the Rhesus monkey spends a tremendously long time displaying day after day a partial complex seizure pattern before they begin to develop motor seizure manifestation. When you look at the electrographic contents of these seizure developments, one is impressed with how quickly the seizure discharge propagates downstream as well as to the dorsal hemispheric convexity in *Papio papio,* in contrast to the afterdischarge contained within the stimulated temporal lobe structures in the Rhesus monkey. One of the factors which was mentioned by the Montreal group with respect to the outcome of surgical treatment of focal epilepsy was the presence of preoperative generalized convulsive seizure which tends to decrease the success rate among patients who are subjected to a localized excision of epileptogenic tissue. It seems to me that we have an interesting experimental model in *Papio papio* and Rhesus monkeys with respect to an absence or presence of predisposition to the generalized convulsive seizure. Our own limited series of 26 surgical cases selected from over 130 radically investigated intractable seizure patients, indicates that if we limit ourselves to the temporal lobe variety, the patient without a history of generalized convulsive seizure seems to have done best. Obviously, in human problems, we do not know what we are dealing with regarding the nature and extent of the pathophysiology but our observations certainly remind us of the necessity to be aware of the importance of genetic predisposition to seizure susceptibility.

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