

CHLOROQUINE TREATMENT IN EPILEPSY*

BY

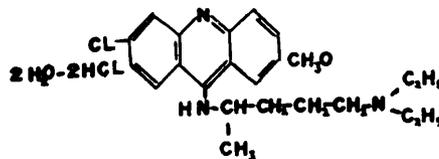
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Mr. Chairman and my colleagues, I have to apologize that there are slight differences in the data between the abstract already delivered and the content of this lecture. I have made re-examination anew in this August, looking for more exact and newer findings.

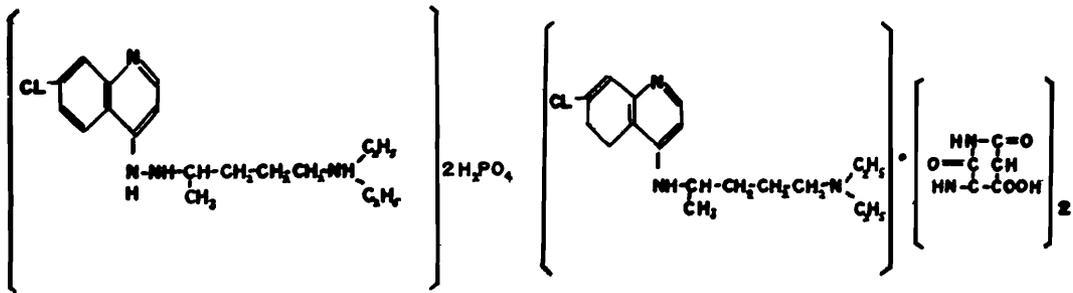
Ten years ago, Dr. Mendez, and then Dr. Lennox, one of my supervisors in old days, tried Atabrine to use in the treatment of refractory petit mal epilepsy, and obtained certain effective results, though it was impossible to deny severe side-effects. Considering this short point of Atabrine, I, since this 2 years, have been engaged in almost the same idea: namely, to use Chloroquine, instead of Atabrine. And, during the course of this experimentation, we happened to see Dr. Vazquez's report on the Chloroquine treatment for petit mal absence. Here I would like to point out that the same idea and its orientation, started independently in South America and Japan:

Fig. 1 Atabrine



Chloroquine diphosphate
(Resochin)

Chloroquine diortate
(Kidola)



As shown in Fig. 1, 2 kinds of Chloroquine, namely the diphosphate "Resochin" and the diortate "Kidola" which is made in our country, were used in this study, but there were no significant differences in practical effect.

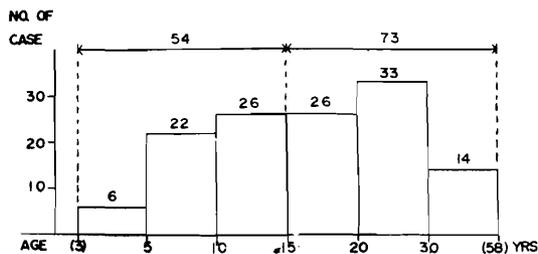


Fig. 2 Age distribution of the subjects which the chloroquine treatment has been applied (127 cases in the total number).

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After many trials, we have decided to treat not only petit absence but various epilepsies with Chloroquine which, as you know, is a new agent for the collagen disease, resembling to Atabrine. As indicated in Table 1, subjects treated are consisted of 127 cases with 157 seizures in the total number : about one-third of them, children (s. Fig.2). For convenience, these subjects were classified into 2 groups (s. Table 1). The "old" group, 112 cases, had been treated with the

Duration (Yrs.)	Below 1	1 2	3 4	5 6 7 8 9	Above 10	New Case	Total
No. of Case	7	41	38	23	3	15	127
	48			64			

Table 1 Duration of therapy with the routine anti-epileptic drugs administered before the chloroquine treatment (112 cases)

routine anti-epileptic drugs from one up to more than 10 years, but with very few or no practical effects, especially due to side-effects or intolerance : they were refractory, indeed, in our hands. In other 15 "new" cases, this therapy has been performed from the beginning.

We defined this therapy as follows : a combined administration of Chloroquine with the routine anti-epileptic drugs, such as Dilantin, Mysoline, Tridione, Diamox, Phenobarbital and so on. Accordingly, in the "old" group, Chloroquine was added only to the basic anti-convulsants administered. No cases were treated with Chloroquine alone, because it seemed to be rather ineffective, as far as our preliminary experiment was concerned. As indicated in Table 2, most of the cases were treated with Chloroquine more than a half year, and the longest is 23 months.

Duration (Months)	1~2	3~5	6~8	9~11	12~16	17~23	Total
No. of Case	12	24	22	15	21	33	127
	(5)		(1)				
	36			91			

Table 2 Duration of the chloroquine treatment in the subjects

() means the cases in which chloroquine had to be withdrawn because of severe side-effects occurred during the course of treatment

Fig.3 is the comparison of clinical effects prior and posterior to this treatment. In each seizure group, there is a shifting of black-circles upwards, when compared with the position of white-circles which show the effects before application of this treatment : this shifting means, without doubt, an increase of efficacy due to application of Chloroquine.

EFFECT	LEFT COL MARKED 0		RIGHT COL MARKED 1		BEFORE		AFTER		TOTAL
	CONVULSIVE	MYOCLONIC	ABSENCE	PSYCHOMOTOR	AUTONOMIC	OTHER	NEW CASE		
COMPLETE CONTROL	0	0	0	0	0	0	0	0	0
EFFECTIVE	45	45	45	45	45	45	45	45	45
UNCHANGED	33	33	33	33	33	33	33	33	33
AGGRAVATED	9	9	9	9	9	9	9	9	9
TOTAL	66 (7)	19 (5)	11 (1)	49 (4)	6 (1)	6 (0)			157 (18)

Fig. 3 Comparison of shifting of clinical effects before and after the chloroquine treatment

Considering not only reduction of seizure frequency, but improvements in various somato-psychical conditions, we, as shown in Table 3, classified the clinical results of this treatment as follows : remarkably effective, effective, unchanged and aggravated ; that is in %-approximately - 20%, 55%, 20%, and below 5% for the above groups. In total, the effectiveness exceeds 70%. It exceeds, also in the subjects with frequent seizures, such as several times a week or even a day.

By the way, at the present knowledge of the routine anti-epileptic drug therapy, as you know well, 20 or 30% of the cases remain, hardly responding to the drugs administered. They are

called as "refractory epilepsy" As you can see in Fig.3, before the Chloroquine treatment, in our "old" cases, effectiveness was found to be only at a rate of 30%, however, afterwards, applying Chloroquine, it increased to 80%, including 46 cases with complete control. This increase, that is a gain of 50%, may indicate the effectiveness of this treatment. In other words, due to application of this treatment, the refractory cases may decrease to about one-half. Here, at this point, I should like to insist upon this efficacy in the Chloroquine treatment, and also, certain possibilities available for clinical practice.

Sz	Effect				Total
	⊕⊕	+	±	-	
Frequent	21	42	16	3	82
Infrequent	12	41	20	2	75
Total	33 (21%)	83 (53%)	36 (23%)	5 (3%)	157 (100%)
	116 (74%)		41 (26%)		

Table 3 Effect of the chloroquine treatment : summarized results

⊕⊕ : Remarkably effective.
 + : effective
 ± : unghanged
 - : aggravated

3 : 1

How are the relations to seizure type? Efficacy due to averaged values was running down from petit absence > convulsive seizure > psychomotor seizure > other seizures. However, among individual cases which showed dramatic effects, the order is as follows : petit absence > myoclonic seizure > psychomotor tonic-arrest seizure > grand mal > psychomotor automatism.

There were no significant correlations between the effect and the dosage of Chloroquine (s. Fig.4). Generally speaking, the low dosage, rather than high one, seemed to be more effective. Of course there were individual differences. Also, among combined anti-epileptic drugs, Diamox seemed to be more effective than other drugs.

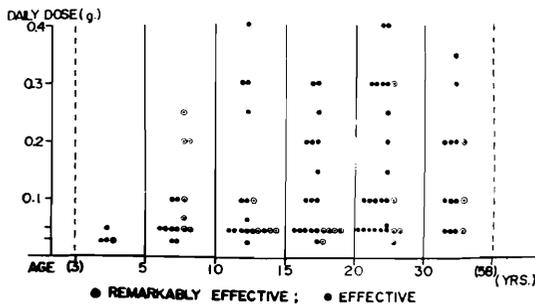


Fig. 4 Relation between age and optimal dose of chloroquine in effective cases.

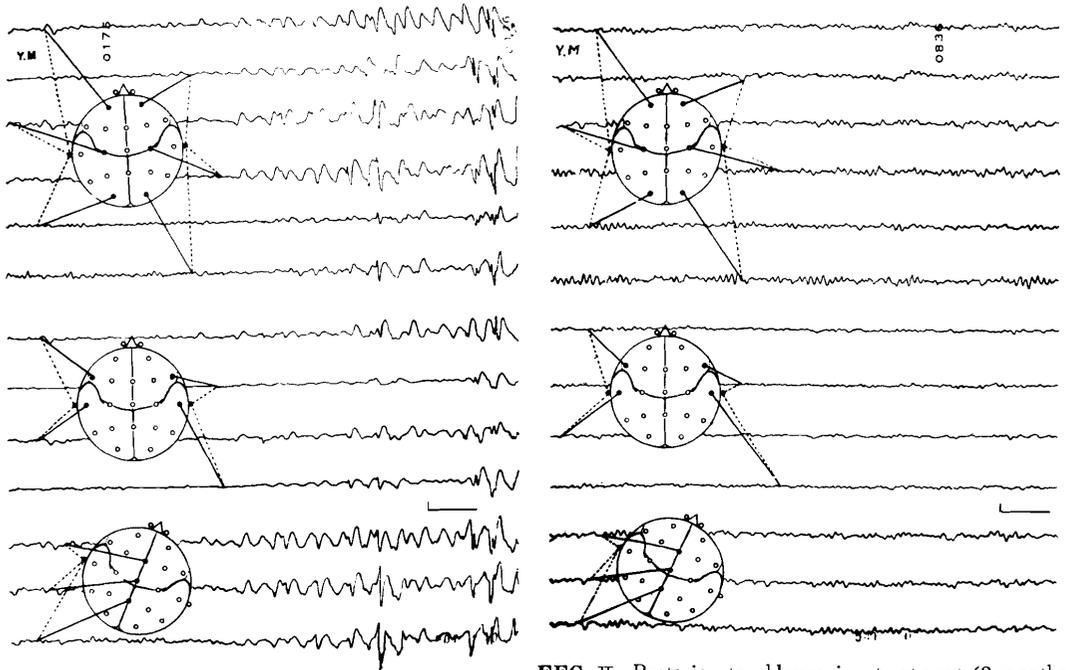
Symptom	No. of Case
Gastro-intestinal Disturbance	11
{ Diarrhea	{ 2
{ Vomitting	
Ophthalmologic Disturbance (Sensation of Felickering)	1
Aggravation of Seizure	2
Total	14

Table 4 Side effects occurred during the course of chloroquine treatment

Side-effects were rather few. As shown in Table 4, most of the symptoms occurred in the gastro-intestinal sphere, and these were transient, tending to disappear soon after interruption of administration. Only in 6 cases, it was impossible to continue this treatment, because of severe side-effects. Transiently, one case complained of ophthalmic disturbance. We also examined

"electro-retinogram" in 10 cases undergoing this treatment above one year, but could not find out any abnormal signs.

Next slides marked as EEG-I & II - this is a comparison of EEGs recorded before and after application of this treatment in the same case. A lot of improvements may find out. Don't you



EEG I. Prior to chloroquine treatment; resting record.

EEG II. Posterior to chloroquine treatment (3 months afterwards); resting record; the same case.

agree with my opinion? In such a way, there, in electroencephalograms, as indicated in Fig. 5, usually occurred significant improvements in most cases, particularly those in the basic rhythm : namely, a strong tendency towards normalization, especially in the results obtained by means of

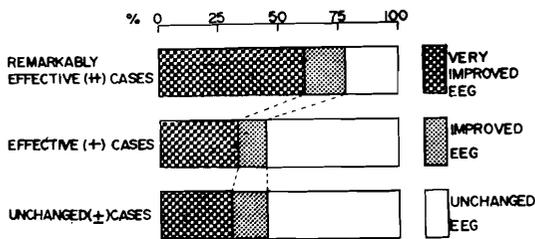


Fig. 5 EEG changes due to the chloroquine treatment: results of general interpretation from the 71 cases, compared with the findings prior to the start of chloroquine administration.

the automatic frequency analyzer. As shown in Fig. 6, there is a decrease of delta-waves and an increase of alpha-waves. This change, I think, may suggest somethings concerning the cerebral mechanism of this treatment.

At last, clinical course in several cases is demonstrated.

Case 1 (Fig. 7) : Petit mal absence. Immediately after administration of Chloroquine, frequent seizures disappeared within 4 days. Also, please take attention about the reduced dosage of Tridione in the later stage of treatment. Thus, there is a supplementary effect of Chloroquine, too.

Case 2 (Fig. 8) : Tonic-arrest seizure of psychomotor type. Even in this case, you can see a quick effect, too. As indicated, however, Chloroquine alone was ineffective.

Case 3 (Fig. 9) : Mixed epilepsy with convulsive and psychomotor seizures. This case showed a severe side-effect, that is to say intestinal paresis, during the course of the treatment, however,

after interruption of administration of Chloroquine, it disappeared. And, then, we could treat again with reduced dosage of Chloroquine.

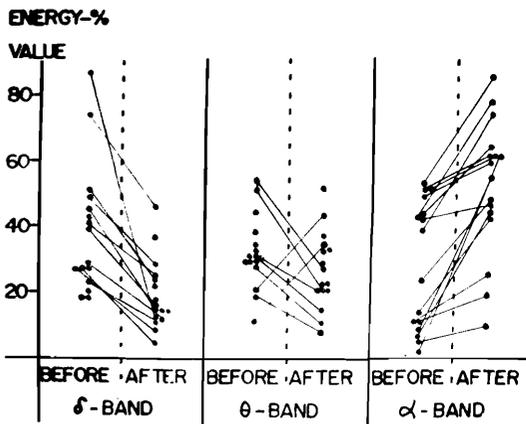


Fig. 6 Results from automatic EEG-frequency analyzer: comparison of energy-% before and after the chloroquine treatment (EEG was recorded from the right occipital area).

Case 4 (Fig. 10) : This is a refractory case having been treated more than 10 years. Figure indicates about two-years course after administration of Chloroquine. Withdrawal of Chloroquine usually introduced relapse. At the present, under Chloroquine, no seizures.

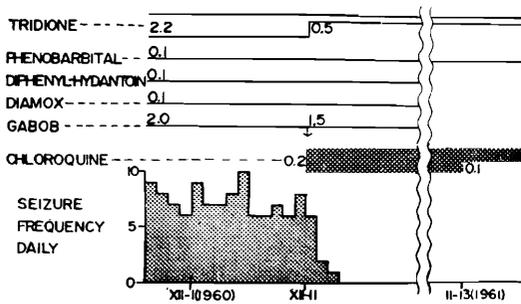


Fig. 7 E. S. (♀, 10 yrs.) Petit mal absence.

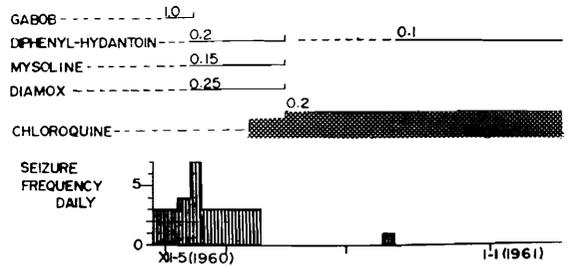


Fig. 8 G. Y. (♂, 9 yrs.) Tonic-arrest seizure.

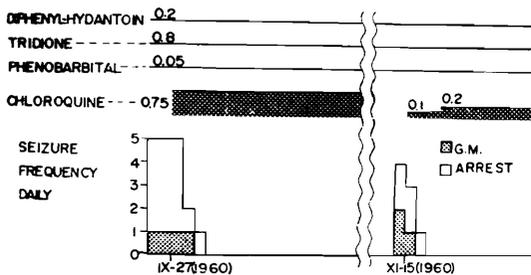


Fig. 9 Y. M. (♀, 9 yrs.) Grand mal & tonic-arrest seizure.

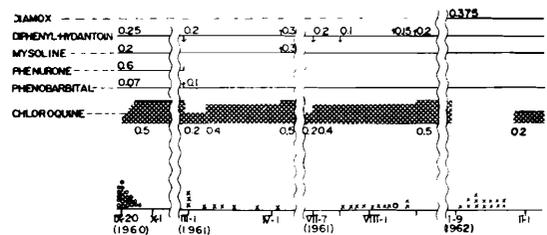


Fig. 10 C. T. (♀, 22 yrs.) Psychomotor-proper (●) grand mal (○) and abortive (arrest) seizure (×)

So - that is all, Ladies and Gentlemen, thanks listening to me.