Acta Medica Okayama

Volume 8, *Issue* 4 1952 *Article* 9

MARCH 1954

Studies on Allergic Genesis of Idiopathic Epi-lepsy

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Abstract

In such animals not having any organic changes in their brains during the initial stage showed a descendence of convulsive threshold. abnormal findings in their electroencephalogram and ascending activity of ChE. But what is the cause of these functional changes? First, from the fact that though there was no organic changes, they were sensitized and reiniected by a known antigen, which is obviously an antigen-antibody reaction. Second, from the fact that we got a histological.change, which was acknowledged as C.L.A. changes by increasing the concentration of these solution and the number of injections, it could be thought that these functional changes were caused by what I called latent C.L.A.. That is, it seems it could be thought that it would give functionally a permanent hypersensitivity, which is called convulsive arrangement. Furthermore, a similar histological findings as seen in old epileptics were made experimentally after prolonged and repeated injections of very diluted antigens. I believe it can be said, also from this histological point that they are experimental epileptics. But I am not trying to say that idiopathic epilepsy is the same allergic disease as asthma. If it was so, it should offer clinically a problem of eosinophilia in the blood of epileptics. But actually there is no eosinophilia in epileptics. Also, in adult epileptics, convulsive attacks is not often seen soon after introduction of antigens. Consequently, my theory that epilepsy is allergic, does not mean that allergy is the direct cause of epileptic attacks. What I mean is, the causal genesis of idiopathic epilepsy is hypersensitivity of nerve cells in the brain. This hypersensitivity was attained as a tissue reaction by some allergic mechanism without any organic changes. This functional change gives the nerve cell a hypersensitive state, which becomes the base of the beginnihg of convulsion. Its inducement of attack could be water stagnation in the body, anemic state of the brain, alkalosis, or introduction of allergens. In short, the cause of attack does not always come from allergic reactions.

Studies on Allergic Genesis of Idiopathic Epilepsy

By

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Received for publication on 1 February 1954.

1.

Before we discuss the genesis of epilepsy, we must define its causes. One is the direct cause, which induces convulsive and psychic attacks (formal genesis). The other is the indirect cause which explains how pathologic conditions, producing these attacks, are made (causal genesis).

Hitherto are two well known groups of theories. One is the vasculospasmodic theory and the other is the intoxication theory. The latter is caused by the disturbance of nitrogen metabolism, by decomposed substances from protein or by auto-neuro-intoxication. Some have pointed out abnormal endocrine of adrenals, genital glands, hypophysis, thyroid, parathyroid and others. At present, there is a theory concerning the unbalanced power of hydrogens, which is supported by many. Unbalanced power of hydrogen and vascular spasm are phenomena found just before attacks and may offer to its direct causes indeed, but their causal genesis concerning to such as the decompensating alkalosis or the so-like rash spasm of cerebral vessels are not yet settled.

When actually observing epileptics, intoxication and abnormal endocrine theories and their pathological situations is difficult to accept as causal genesis.

The next problem with idiopathic epilepsy is that it has more or less relations with their family heredity and constitution. We must keep in our mind that there is something that starts fits which are based on their epileptic constitution. Because, during craniotomy we occasionally experience cases of traumatic epileptics in which we do not find any organic changes, while on the hand, we have cases with severe cicatrized adhesions and still with no epileptic fits. When healthy ones take a deep breath, more than 10% of them shows an abnormal electro-encephalographic waves similar to those found during interval periods of idiopathic epileptics. (*Gibbs*, *Gibbs* and *Lennox*, *Katsura*). From these points, it seems that to study

the cause of epileptic constitution and its convulsive arrangement would be the key to solve the causal genesis.

2.

The idea that idiopathic epilepsy arises from allergy, particularly, food allergy has already existed since the beginning of this century. In 1904 *Spratling* suggested that food idiosyncrasy could cause epilepsy. But it was actually shown for the first time by *Pagniez* and *Lieutaud* in 1919. They found a patient who had convulsions when eating chocolate and that he was relieved from it when he was given a very small amount 45 minutes prior. In 1922 *Ward* said that the cause of epilepsy must be protein sensitization. Besides him there were many, such as *Ward* (1922), *Howell* (1923), *Wallis, Nicol* and *Craig* (1923), *McCready* and *Ray* (1924), *Ball* (1927), *Rowe* and *Richet* (1930), *Wilmer* and *Miller* (1934), *Forman* (1934), *Balyeat* (1928), *Winkelmann* and *Moore* and others who had observed epileptic convulsions induced by food allergen and which were controlled by limiting their usage. *Howell* (1923), *Ward* and *Patterson* (1927), *Beauchemin* (1936) and others have reported that dermatologic reaction by food antigens were positive in epileptics. Especially, *Beauchemin* described distinct skin reactions by extracts from various endocrine organs.

It seemed as if the idea that epilepsy may be caused by allergy rose from its many resemblance to migraine. From family histories *Buchannan* (1921), *Ely* (1930), *Stiefler* (1924) showed the coexistence of migraine and epilepsy. Again *Spangler* (1927), *Balyeat* (1928), *Adamson* and *Sellers* (1933) and others showed from the point of family histories that some allergic diseases such as asthma, urticaria, hay fever, dermatitis and others, besides migraine appeared more than usual in these families. But, it is admitted by all that from the view of family histories, the percentage of occurrence of other allergic diseases are much lower in epilepsy than in migraine, hay fever, asthma of others. *Clarke* says that convulsions seen in infants are caused mostly by allergy. In conclusion, dermatologic reaction is not always so exact in epilepsy as in other allergic diseases. *Vaughan* says in his book "Practice of Allergy" (1948) that idiopathic epilepsy should be described as non-allergic in principal but at times it could be regarded as allergic,

particularly in food allergy when it has an effect as a secondary factor. Recently *Rosenow* (1947) was able to divide a stock of 'alpha'-streptococcus from the naso-pharyngeal cavity of epileptics, used it for intradermal reaction and had a result of 96% positive in idiopathic epileptics. *Bering* (1951) repeated the test again and reported that in normals only 6.7% reacted positive while in idiopathic epileptics it was 78.8%. He reported that this reaction was negative in organic epileptics. When this intradermal test was repeated with 'alpha'-streptococcus from migraine and arthritic patients, it showed no significant difference between idiopathic epileptics and their contrasts. He also said that this intradermal reaction agreed with electroencephalographic readings.

3.

Now I would like to mention the beginning of our study.

The first starting point was from the question what is epileptic constitution. Then what is convulsive arrangement when we think only of convulsion. As it is easily understood by electroencephalographic reading taken during the intervals of epilepsy, the nerve cells concerning convulsion are in a hypersensitive state. Then another problem comes up, is this congenital or acquired, as the heredity of epilepsy is not so dominant, it is easier to think that it is transmitted more humorous than by chromosomes or genes.

Next, as idiopathic epilepsy is defined as an epilepsy without any organic pathology, we have tried to make a hypersensitive state among nerve cells by some method without giving them any organic change. As it is well known, idiopathic epilepsy too, has a definite organic change in its terminal stage.

In the beginning there is a functional hypersensitive without any histological changes, but after repeated attacks a chronic and organic changes develops. If these changes could be considered as an allergic disease it would be most reasonable. By repeating weak allergic reactions it was believed that this epileptic condition could be accomplished. Of course, acute allergic findings in the cerebrum (serologically, the reaction in a local tissue caused by a known allergen is called local anaphylaxis, so from here on this reaction in the cerebrum will be called cerebral local anaphylaxis, viz., C. L. A.) shows the picture of allergic encephalitis and not tha

of idiopathic epilepsy. What I planned to make was, of course, not this allergic encephalitis but a very weak chronic allergic state without any organic change in the cerebrum. Accordingly, I have called this reaction as latent cerebral local anaphylaxis. In addition to this, I hope the reader would read my short paper in Nippon Rinsho Vol. 9, No. 12.

There are many methods in making artificial C. L. A. such as by using various antigens and giving effective injection into the cerebrum, or by pasting various allergens on the surface of the brain after general sensitization. Or by giving effective injection intravenously after the brain had been sensitized (*Davidoff, Kopeloff* and *Kopeloff, Seegal* and *Seegal, Davidoff* and *Kopeloff, Tokushige*), or by giving effective injection into the carotid artery after general sensitization (*Miyahara, Nakanishi*), or by giving both sensitizing and effective injection into the cisterna (*Akamatsu, Iwasa*), or by using sera added with cerebral phosphatid (*Maekawa, Sawami*), or by using an emulsion of the brain mass (*Rivers, Sprunt* and *Berry, Rivers* and *Schwentker, Freund* and *McDermott, Pacella* and others). And not a few have observed spontaneous convulsions in animals by these methods, but they were planned to make distinct organic change in the brain caused by local anaphylaxis which were very different from our purpose.

4.

To satisfy my purpose in making latent C. L. A. I used rabbits because they are difficult to get histological changes by local anaphylaxis (*Kopeloff, Tokushige*). As antigens, I employed egg-white solution (1), non-effective cow sera (2), and cow sera added with cerebral phosphatid taken from cow's grey substance in the brain (3).

The first two, (1) and (2), were injected into the carotid artery after subcutaneous sensitization and when using (3) both sensitization and effective injections were done intravenously, expecting the organ specificity of the cerebral phosphatid to work.

1. *Histological findings* (*Sakakibara, Kasai and Shimizu*).

(1) 10 to 20 days after subcutaneous sensitization with egg-white, 2 cc. of double diluted egg-white was injected into the carotid artery every ten days for three times. In these the follow-

ing findings, which would give a distinct picture of local anaphylaxis, were observed in the brain parenchym. That is, diffuse hemorrhage, loss of blood circulation in the small vessels, stagnation of plasma, infiltration of leucocytes in the surrounding of vessels, capillaritis, dissolution of vessel wall tissue, acute simple degeneration of nerve cells and others. When four times diluted egg-white solution was injected, there were only a few findings which seemed as a slight congestion and there were no pathological changes in the small vessels nor among the nerve cells.

(2) Two weeks after sensitization with cow serum added with phosphatid taken from the grey substance of the cow's cerebrum and which was injected intravenously, this again was repeated at the rate of 1 cc, per kilogramm every two weeks for ten times. In such cases, there was a picture of loss of circulation in the arterioles, angiitis among the capillary vessels, an acute simple degeneration among the nerve cells. The myelin sheath showed that they did not drop off though they were quite disturbed. When a double diluted solution of egg-white was used the picture was not as significant as this, but it was enough to show an obvious picture of C. L. A. In cases where they received only five effective injections the picture of light congestion and no findings of C. L. A. was observed. That is, in the first case by using a four times diluted solution and in the latter case by decreasing the number of injection to five times, there was hardly any changes histologically.

2. *The threshold of convulsion by cardiazol* (*Sakakibara, Kasai and Shimizu*).

To prove that these rabbits have become idiopathic epilepsy, that is, that they have gained the convulsive arrangement, it was difficult to find spontaneous convulsions (This was observed accidently in only one case). So provocative method was used to define the rabbits threshold to it.

The results were as follows. For contrasts normal rabbits and unsensitized rabbits that only received effective injections were used. In these there was hardly any decline in their threshold (Fig. 1).

Those which were only sensitized showed some decline but it was never below 80% (the threshold before sensitization was considered as 100%) (Fig. 2).

Fig. 1. Group of non-sensitized—Group receiving only 1 injection in the carotid artery.

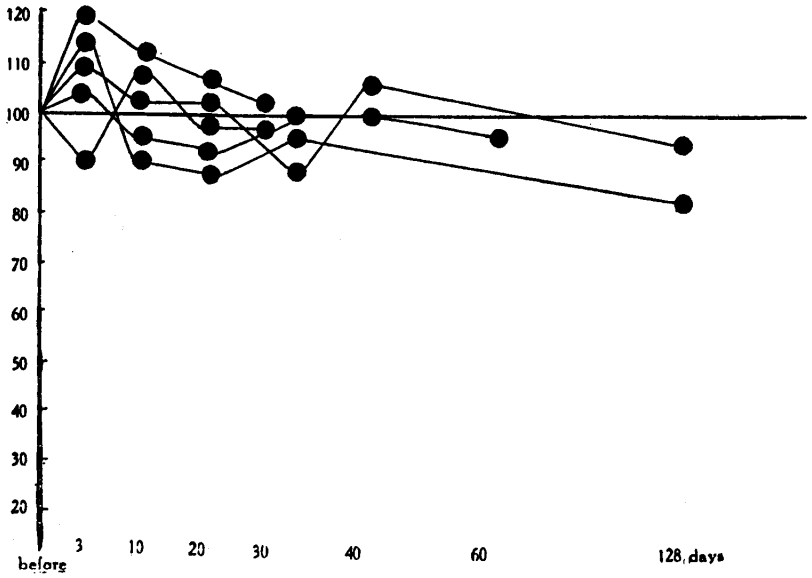
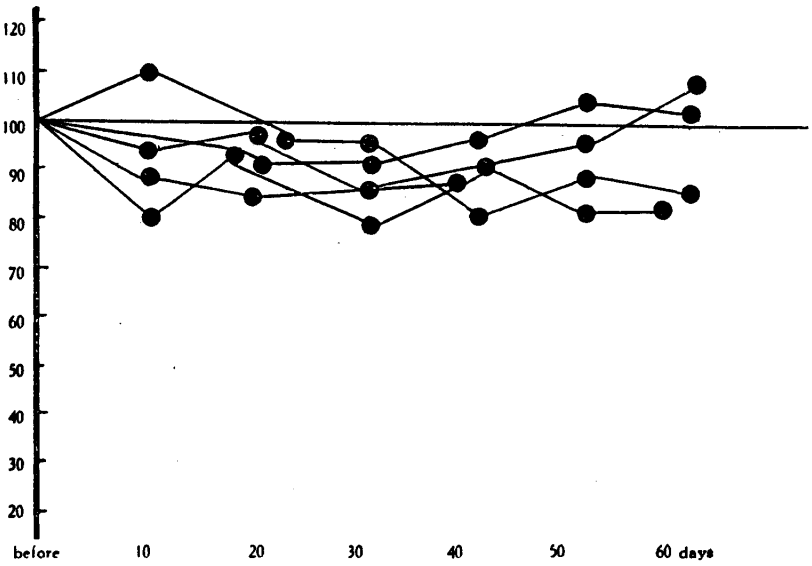


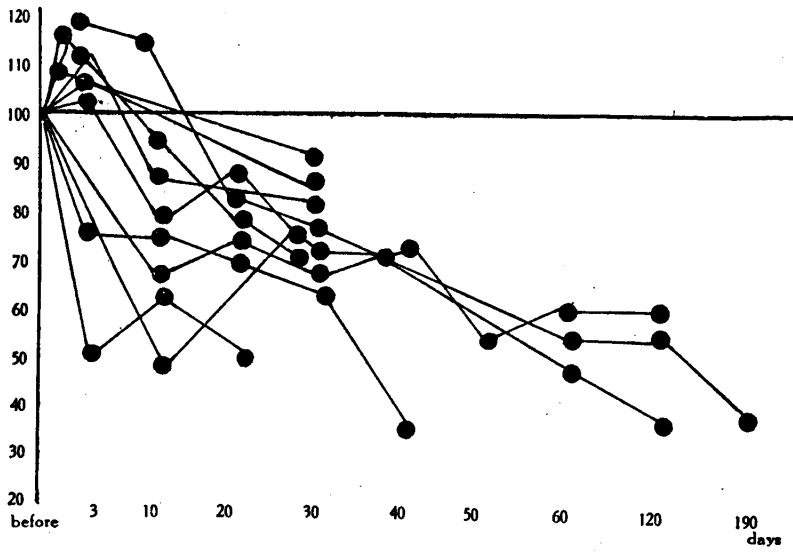
Fig. 2. Group which had only subcutaneous sensitization.



But in those which received effective injection after sensitization, there was a slight incline on the third day but after that a

sharp drop was observed and in cases which lived as long as 120 and 190 days there was no evidence of reascending (Fig. 3).

Fig. 3. Group of subcutaneous sensitization—Receiving 3 effective injection in the carotid artery.



This was more significant as the number of injection increased.

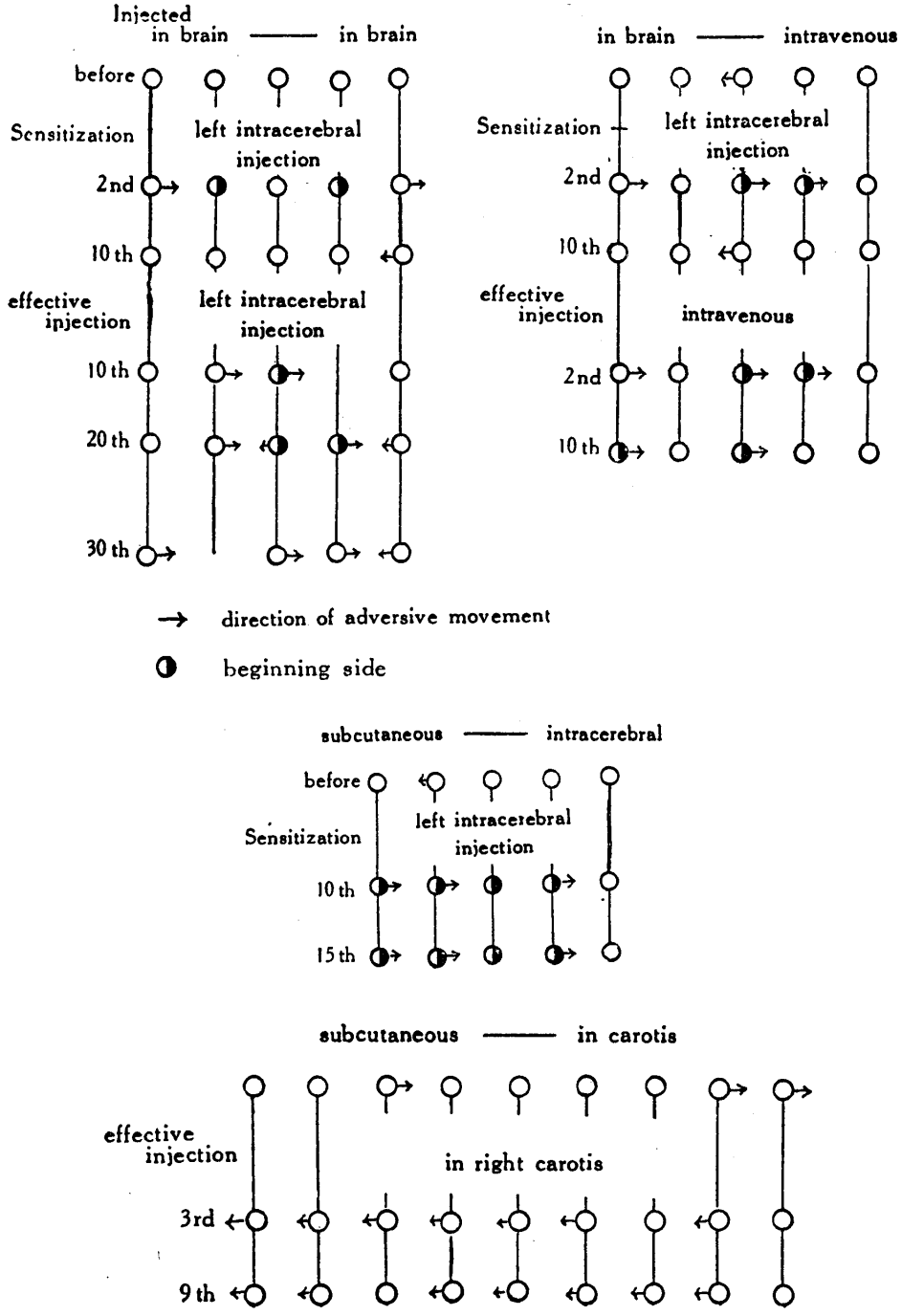
3. *The beginning side of the convulsion and the direction of the adversive movement* (*Sakakibara*).

Convulsion was provocated by injecting cardiazol intravenously in rabbits which had latent C. L. A. on one side of the brain and the beginning side of the convulsion and the direction of the adversive movement was observed to see if they were focalized or not.

Four method were used in the experiment, (1) unilateral intracerebral sensitization and isolateral intracerebral effective injection, (2) unilateral intracerebral sensitization and intravenous effective injection, (3) subcutaneous sensitization and unilateral intracerebral effective injection and (4) subcutaneous sensitization and effective injection to one carotid artery. Intracerebral injection was always done into the posterior part of the olfactory bulb and the anterior end of the motor area.

The result of the experiment is as shown in Fig. 4..

Fig. 4.


Injected
in brain —— in brain
before
Sensitization
left intracerebral injection
2nd
10th
effective injection
left intracerebral injection
10th
20th
30th
in brain —— intravenous
Sensitization
left intracerebral injection
2nd
10th
effective injection
intravenous
2nd
10th
→ direction of adversive movement
beginning side
subcutaneous —— intracerebral
before
Sensitization
left intracerebral injection
10th
15th
subcutaneous —— in carotis
effective injection
in right carotis
3rd
9th

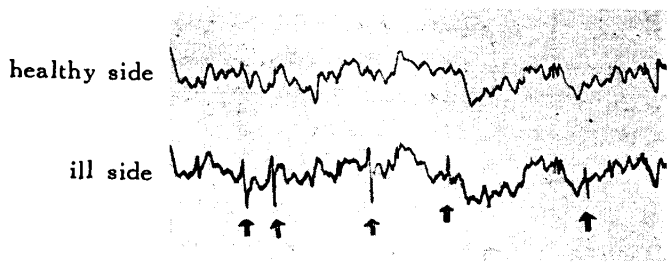
In cases with only intracerebral sensitization the beginning side of the convulsion and the direction of the adversive movement was opposite to the side of the injection, but this was temporary. After ten days it returned to the same condition as it was before sensitization. Great majority or those which received effective injection did not change even after the tenth day and the condition remained on the opposite side of the injection. What was interesting was that in group four (4) that is, those which received effective injection on one side of the carotid artery showed a much more definite focus when they received just one effective injection than receiving multiple numbers of injection. This is probably, as the number of injection increases the solutions passes through the communicating artery to the other side and makes other focuses in the opposite hemisphere and the brain stem. This blurrs the picture.

4. *Findings by electroencephalogram* (*Sakakibara*).

Rabbits show remarkable individual difference in their E. E. G. And as there was no meaning in comparing the E. E. G. of normal rabbits to those having latent C. L. A., E. E. G. was taken from the same rabbit that were used in the previous experiments, which had latent C. L. A. just on one side. The E. E. G. was recorded from both sides at the same time at the height of the upper part of os nasalis and from the skin.

The results were as follows: With just sensitization, E. E. G. showed no abnormality and there was no difference in the E. E. G. taken from both sides when activated with cardiazol. But those which received effective injection showed definite spikes on the ill side Fig. 5.

Fig. 5.



When their convulsions were provocated with cardiazol, convulsion waves appeared on the ill side, first (Fig. 6),

After convulsion there was a definite phenomenon of fatigue in the E.E.G. which appeared earlier and remarkably on the ill side (Fig. 7).

Fig. 6.

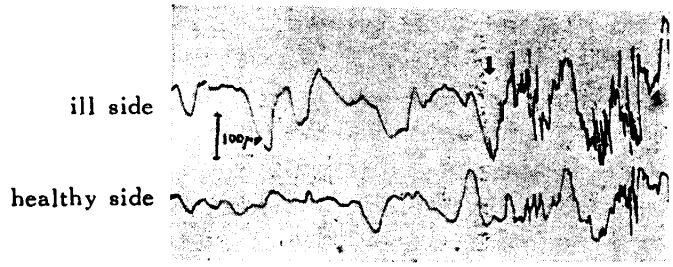
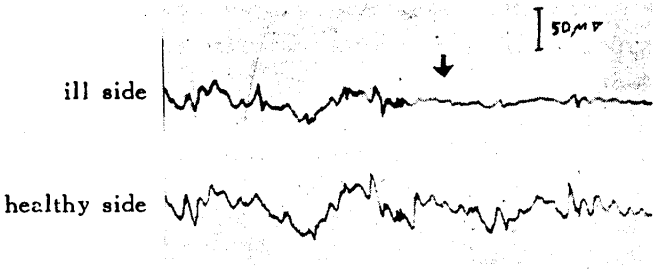


Fig. 7.



These changes were seen in about half of the cases. This was never positive on the healthy side. This was also not temporary and was seen seven months later in the same cases.

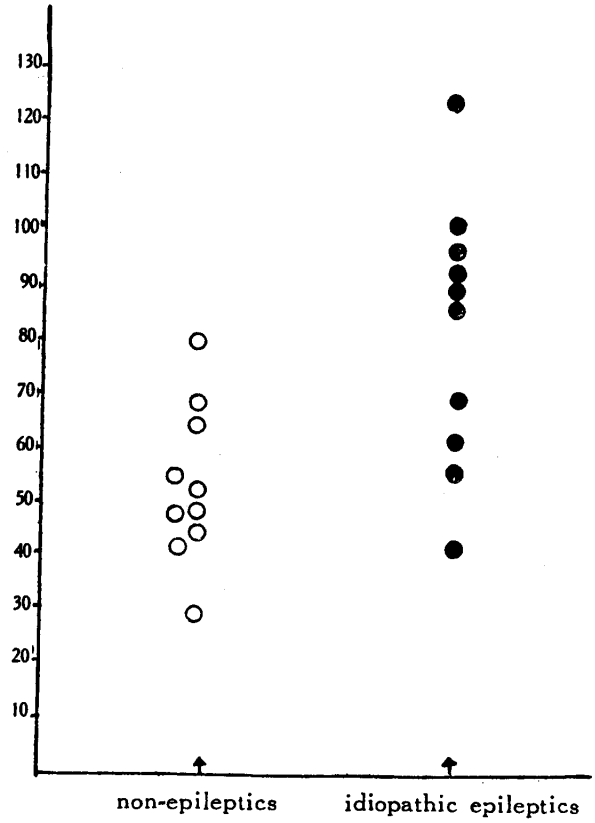
5. *Activity of Cholinesterase* (*ChE*) (*Oki*).

It is obvious that the metabolism of acetylcholin must be unusual in the brain where there are violent attacks such as epileptic convulsions. It is a known fact since *Nachmansohn* that by measuring the rate of activity of ChE, which is relatively stable, Ach's alteration could be understood. *Pope*, *Morris*, *Jasper*, *Elliot* and *Penfield* (1947) also proved that the rate of activity of ChE was much higher in the focus of the epileptic brain than in any other parts.

Fresh brain tissues were taken from resected cerebral cortex of patients who were having craniotomy. These patients were idiopathic epileptics and non-epileptics, such as athetosis and psychological patients. To measure the rate of activity of ChE both types

of brain tissues were made into 50 times diluted emulsion and *Warburg*'s manometer was used. And as in Fig. 8.

Fig. 8. Activity of ChE.
(CO_2 cmm/Fresh Tissue 100 mg 30 min.)—human cerebral cortex.



The rate of activity was usually much higher in idiopathic epileptic brains than in their contrasts. When brains from rabbits having latent C.L.A. and normal ones were compared, the result were as in Fig. 9, that is, the rate of activity was higher in the former ones.

When this was compared among the groups taking various kinds of egg-white solutions, usually as the number of effective injections increased, the means grew higher. When a comparison was made in brains of animals receiving effective injection in the carotid artery of one side, though there may be extra-ordinaries, the

rate of activity of ChE was usually higher on the side of the brain which received effective injections. See Fig. 10.

Fig. 9. Activity of ChE.
(CO_2 cmm/Fresh Tissue 100 mg 30 min.)—in rabbit's cerebral mantel.

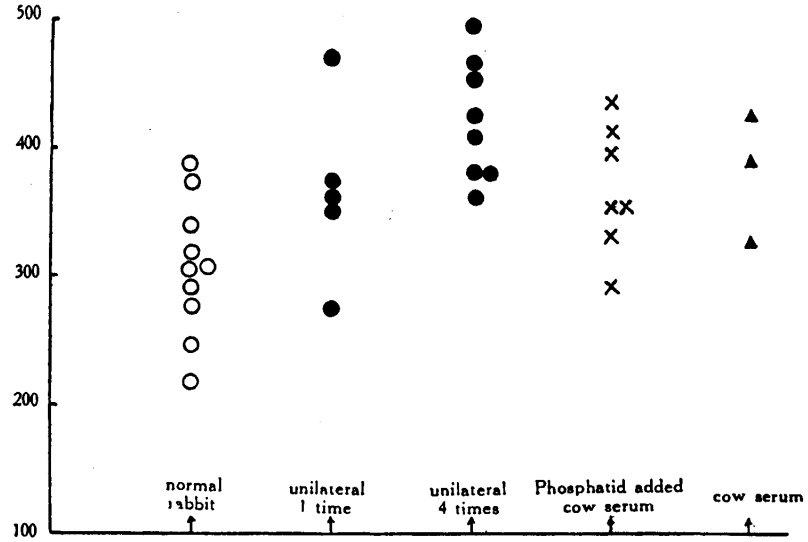
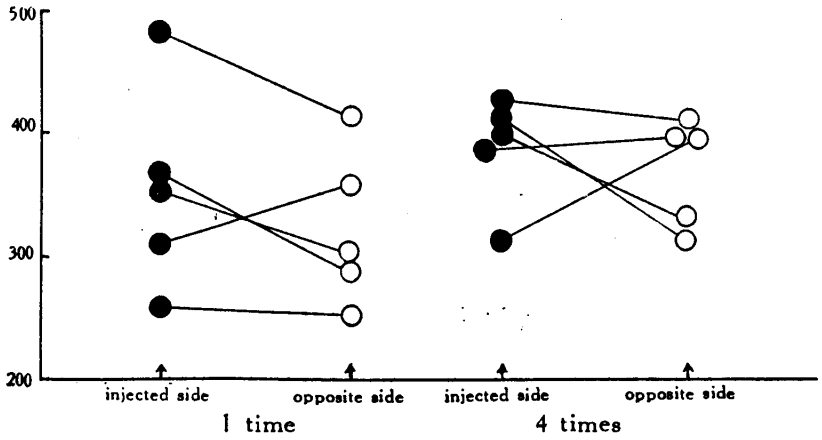


Fig. 10. Activity of ChE.
(CO_2 cmm/Fresh Tissue 100 mg 30 min.)—C.L.A. rabbits injected with 4 times diluted egg-white once on one side—Comparison of l. & r. hemisphere.



That is, even in rabbits with latent C.L.A., which were made experimentally, the rate of activity of ChE was higher, as they

were in brains of idiopathic epileptics. From these results it can be thought that the metabolism of Ach is accelerated.

6. *Sugar metabolism* (*Shimizu and Kanematsu*).

1) Irrigation test (*Shimizu*).

In this test the cerebrum of decapitated rabbits and which were kept alive by irrigating fluid were used.

This method was originated by *Inoue* of this department. A comparison in sugar metabolism was made between the cerebrum of normal rabbits and those with latent C.L.A. First, when they were irrigated with solution added with glucose for thirty minutes and the results were as in table 1.

Table 1. Addition of glucose. (mg/dl)

		before	after	decrease
Normal rabbits		138	76	45%
		145	84	43%
		142	85	41%
		145	94	39%
		128	82	38%
		143	94	35%
		mean		41%
C.L.A. rabbits	Cow serum	121	92	24%
		102	79	23%
		193	155	20%
		110	89	20%
		156	128	18%
		103	86	17%
		mean		20%
	Phosphatid added Cow serum	135	99	27%
		110	82	27%
		143	120	17%
		168	137	19%
		mean		22%

In normal rabbits the usage of glucose was an average of 41% while in latent C.L.A. rabbits it was only around 20%. When the amount of pyruvic acid was measured in the irrigating solution before and after irrigation, the results were as in table 2. Latent C.L.A. rabbits showed a much lower mean than those from normal rabbits and from this it can be considered that the decomposing process of glucose to pyruvic acid was greatly restrained. Next, when pyruvic soda was added to the solution and irrigated for thirty minutes the results were as in table 3.

Table 2. Amount of pyruvic acid after fluid irrigation with glucose. (mg/dl)

	before	after	increase		before	after	increase
In normal rabbits	1.20	4.20	3.00	In C.L.A. rabbits	1.10	1.40	0.30
	1.10	5.00	3.90		0.60	1.60	1.00
	0.90	3.20	2.30		0.60	0.70	0.10
	0.90	2.80	1.90		0.45	1.90	1.45
	0.60	2.40	1.80		0.45	2.00	1.55
					0.35	1.80	1.45
	mean		2.58		mean		0.975

Table 3. Fluid irrigation added with pyruvic soda. (mg/dl)

	before	after	increase		before	after	increase
Normal rabbits	7.1	4.4	38%	C.L.A. rabbits	6.8	5.5	20%
	7.3	4.9	33%		7.5	6.1	19%
	7.1	4.8	33%		7.0	5.8	18%
	6.9	4.7	32%		7.4	6.2	17%
	6.9	4.8	31%		7.1	5.9	17%
	7.4	5.3	28%		6.7	5.2	14%
	mean		32%		mean		17%

That is, the rate of usage was 32% in normal rabbits, while in latent C.L.A. rabbits it was 17% and the decomposing process of pyruvic soda was disturbed.

By this irrigating test, sugar metabolism in general was disturbed in the cerebrum of latent C.L.A. rabbits.

The rate of usage is shown as follows. The difference of before and after the irrigating solution was divided by the number gotten before irrigating and multiplied by 100 to get the percentage. The increase of pyruvic acid by the decomposition of glucose were compared with the difference of before and after irrigation.

2) *Glycolysis by slices of cerebral cortex* (*Kanematsu*).

When a comparison was made between the slices of the cortex

Table 4.

Patient	sex	age	date	Q_{O_2}	$Q_M^{O_2}$
Non-epileptics					
I.S.	♀	58	IX	−8.0	6.2
T.I.	♂	61	IX	−7.3	—
H.O.	♀	26	XI	−8.1	5.8
D.M.	♀	13	XI	−8.3	—
mean				−7.9	6.0
Epileptics					
A.U.	♀	20	IX	−7.8	—
S.K.	♀	10	X	−7.5	—
H.U.	♂	17	VI	−8.4	—
E.K.	♂	25	IX	−8.6	—
K.N.	♀	13	IX	−6.1	—
O.N.	♀	17	XI	−7.0	—
D.Y.	♂	11	X	—	5.3
S.T.	♂	6	X	−8.2	5.5
I.M.	♀	6	X	−8.1	4.1
R.K.	♂	24	XII	−7.4	6.9
M.U.	♀	10	II	−6.5	4.9
T.S.	♂	23	III	−6.4	6.1
H.G.	♂	25	III	—	5.3
mean				−7.4	5.4
percentage to non-epileptics				93%	90%

Table 5.

Case	sex	weight	month of experiment	Q_{O_2}	$Q_M^{O_2}$
Normal rabbits					
I	♂	2.5	XII	−7.5	8.0
II	♀	2.0	III	−7.7	5.4
III	♂	2.1	XII	−8.0	6.0
IV	♂	2.4	XII	−7.6	7.5
V	♂	2.0	XI	−7.5	7.6
mean				−7.6	6.9
C.L.A. rabbits					
I	♂	2.4	XII	−7.3	7.1
II	♂	2.0	XII	−7.1	5.0
III	♂	2.0	XII	−8.0	6.2
IV	♂	2.0	XI	−7.2	6.8
mean				−7.4	6.2
percentage to normal rabbits				97%	89%

taken from epileptics and non-epileptics the results were as in table 4.

There was not much difference. Next, when a comparison was made between the slices of the cortex taken from latent C.L.A. rabbt's and normal rabbits the results were as in table 5 and there was also not much difference. (It can be said there was a slight restrainment in the brains from epileptics and latent C.L.A.)

7. Tissue respiration in cerebral cortex (*Kanematsu*).

As in table 4 and 5, when measuring with *Warburg*'s manometer, there were no significant difference between epileptics and non-epileptics, or between the brains from latent C.L.A. and normal ones.

As stated above, there was no significant difference in glycolysis and tissue respiration among the tissue slices taken from various cortex. *Elliot* and *Penfield* also states that there were not much difference between epileptics and normal brains. . But why was it that there was such a significant difference during the irrigation test in latent C.L.A. rabbits?

From the fact that allergic changes in the tissue appears mainly among the vessels system, it could be thought that it was the result of the might be obstruction and stenosis in the very fine capillaries, difficult to detect under microscope, which caused decrease in the blood circulation, or if there were no changes in the capillary vessels there was some kind in the ground substance, called *Nissl*'s grey substance, which fills the space between the vessels and the nerve cells. What I am driving at is that it might be a problem that it is not an allergy of the brain but that of the brain vessels. Therefore, at the present moment we are studying the blood filling and containing condition in the brain vessels with *Campbell-Wake*'s method of manifestating peripheral vessels. I am also studying the condition of the peripheral vessels by injecting synthetic resin.

8. *Amount of free amino-nitrogen in the cerebral cortex* (*Inoue*).

Previously *Inoue* had reported that the amount of free nitrogen in the motor cortex was smaller in epileptics than in non-epileptics (Oct. 1950, at the 4th of the Japan Neurosurgical Society), but at that time we were provocating convulsions by injecting cardiazol three days before the main operation to decide the side of the operation. Therefore, I have come to a question, was the result I have just stated really caused by convulsion or was this because the patient was fundamentally epileptic. To answer this question, we also studied the brain of epileptic patients who did not receive provocation before operation and those who had convulsive attacks during operation and the result is as in Fig. 11.

It obviously show that it was highest in non-epileptics, next, in patients who did not have provocation and the lowest were those who had convulsive attacks during operation. This result tells that it was mainly caused by convulsion.

As in Fig. 12, the result was the same in rabbit's brain. It was the highest in normal rabbits, the next were rabbits with latent

C.L.A. and the lowest in rabbits who just had a convulsive attack.

Fig. 11. Value of free amino-N in human cerebral cortex.

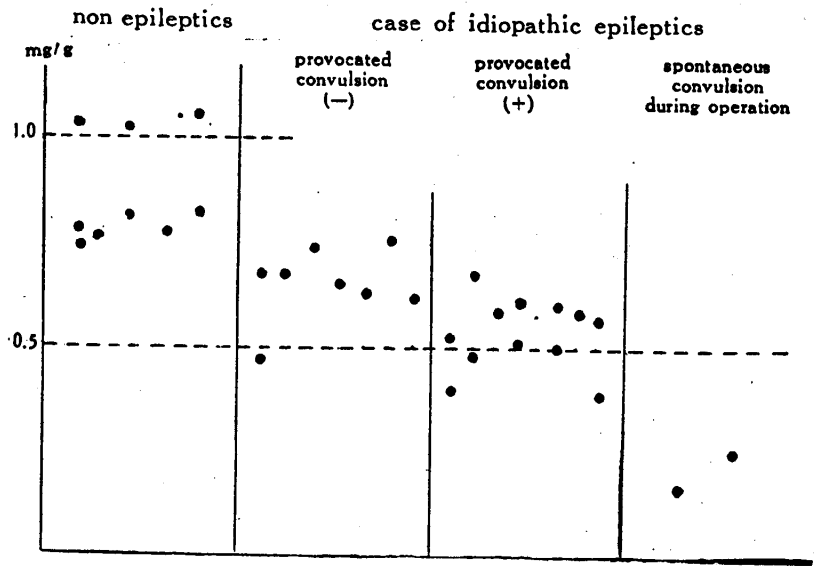
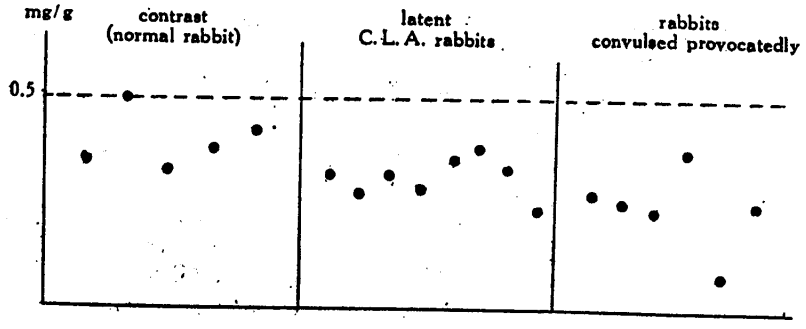


Fig. 12. Value of free amino-N in rabbits brain.



9. Spasm of cerebral peripheral vessels (*Nishimoto*).

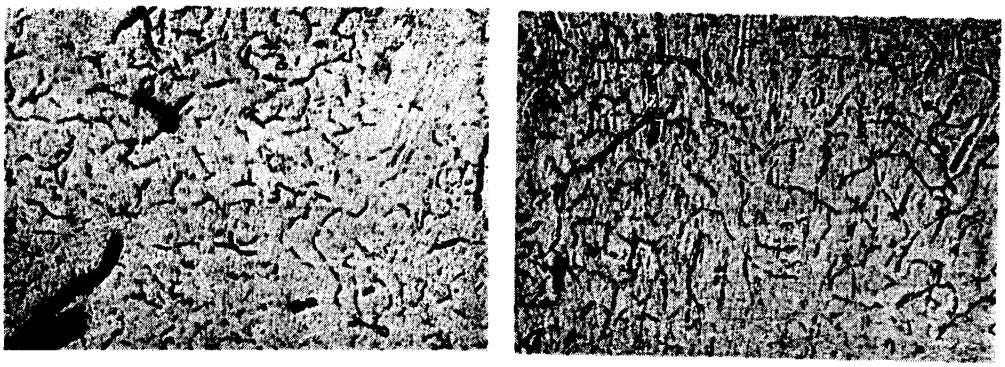
Glycolysis can not be controlled experimentally in vitro when using *Warburg*'s apparatus, but why is it that it is remarkably controlled in vivo during fluid irrigation in latent cerebral local anaphylactic rabbits? From the well known fact that allergic changes occur mainly around the vascular system, it seems as if there is a decrease of blood circulation caused by stenosis or stoppage of fine capillary vessels which can not be found out under microscope.

Standing from this point, I have made an experiment with *Campbell-Wake*'s benzidine method to represent capillary vessels. In the motor cortex, it was found that they were torn off in latent C.L.A. cats, as shown in Fig. 13. Fig. 14 shows the same figure in nucleus lenticularis which is very similar to the picture during preconvulsive stage mentioned by *Scholz*.

Fig. 13. *Campbell-Wake*'s benzidine method (motor cortex).

Latent C.L.A. cat (1 week) Normal

Fig. 14. *Campbell-Wake*'s benzidine method (nucleus lenticularis).

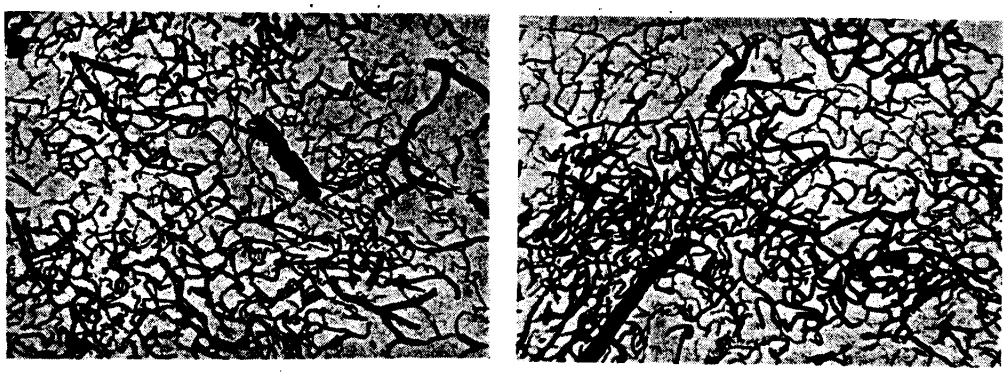


Latent C.L.A. cat (1 week) Normal

Furthermore, Gutta percha was injected to make it clear if this was due to stenosis of capillary vessels or to see if it was merely a functional spasm. This goes into very fine vessels where only one

erythrocyte can barely pass: Its pictures, as in Fig. 15, shows almost no difference between normal and latent C.L.A. cats.

Fig. 15. Gutta percha (motor cortex).



Latent C.L.A. cat (1 week) Normal

It seems as if it is a little too hasty to come to conclusions from this result, but I think it is better to believe that it is caused more by functional spasm than by organic ones.

10. *Structure density of Nissl's grey substance* (*Nishimoto and Shinyama*).

If it can be said that there is a functional spasm without any organic changes in the capillary vessels, it can be thought that there is some change in the ground substance, called *Nissl*'s grey substance which fills the space between capillary vessels and nerve cells. To study this structure density, a mixture of Anilin blue, Ponseau 4R and Orange-G were used for staining because the largeness of these molecules were all different. When density was rough, molecules up to the largeness of anilin blue, which has the largest molecule, was able to enter and it stained specimens blue, but when it was fine only the smaller ones entered and stained it stronger towards red. As its result, up to the second month after the last effective injection, the tissue was rough in latent C.L.A. rabbits and it stained stronger towards blue. At its third month the tissue became as same as its contrast in its density and after 6 month the tissue became more dense in latent C.L.A. and the color showed a tendency to give a stronger red. That is, the rough density seen till the second month was probably due to brain

edema. Later, the tissue became thicker and the transmissibility of *Nissl*'s grey substance became bad. For this reason it is thought that the usage of glucose is depressed during fluid irrigation.

11. Nucleic acid in nerve cells (*Tachibana*).

If animals which have been managed in this way should have a hypersensitive condition, it can be thought that some changes could be found during the activity of the nerve cell. Viewing this point, ketoenol granules which consists of low molecular desoxyribo-nucleic acid and lipoid were stained by *Hamazaki*'s carbol-fucsin jod method. As its results, it was found that in normal cats there were from several to a score of round granules in the protoplasma. In cats with latent C.L.A., there was quite an increase of these granules and as it went into deeper layers of the cortex the increase was more striking. This was most distinguished in the large pyramidal cells. Ketoenol granules in *Nissl*'s grey substance were seen in normal cats as wedged granules sticking on nerve fibres, but in latent C.L.A., it showed a remarkable decrease. Corrosive sublimate ketoenol was identical, too. It is thought that this increase of ketoenol granules in nerve cells is from an acceleration of cell function. And it can also be understood that the decrease of ketoenol granules in *Nissl*'s grey substance is due to its usage. The fact that they showed a remarkable increase, particularly in large pyramidal cells, was significant enough to think that there was a decline in the threshold of cardiazol convulsion. Ribo-nucleic acid and desoxyribo-nucleic acid were examined next, but they showed almost no difference from normal ones. There was a remarkable decrease in strong latent C.L.A. which showed degeneration among nerve cells.

12. Changes in the histological figure when using diluted antigen for a prolonged period (*Sakai*).

In previous parts, I have discussed about the sensitivity in experimentally made so-called latent C.L.A. animals which showed no organic changes, or in their convulsive arrangement state and which were similar to clinical idiopathic epileptics from various ways. They are different in one point. The histological picture seen in old epileptics is not at all an allergic change as we have stated previously. Its pathological degeneration shows distinctly, it is mainly of gliose and this degeneration is now considered as the result of repeated convulsive attacks. Therefore, I

thought I might be able to reproduce a similar histological picture by giving repeated effective injections of a very diluted antigen for a long period. I used 4 to 6 times diluted cow sera added with cow brain phosphatid solution and it was injected every 4th day for 60 to 70 times, that is, for a period of 9 to 10 months. The result is as seen in Tables 6–11. Histologically, in latent C.L.A. rabbits there was an increase of glia and there were findings of marginal gliosis which is regarded specific to epileptics. Along the surface of the brain, dimming of myelin sheath and demyelination were observed.

Table 6. Changes in the motor and frontal areas.

	Epileptic brain	In chronic C.L.A. rabbit brains							
		4 times diluted solution					6 times diluted solution		Original solution
		3rd month	4th month	5th month	8th month	10th month	5th month	9th month	2nd month
Nerve cells	Disappearance			+	+	+		+	+
	Disturbance of arrangement			+	+	+		+	+
	Atrophy				+	+			
	Vacuolar changes				+	+		+	
	Young type				+	+			
	Swelling			+	+	+		+	+
	Edematous changes			+	+	+		+	+
	Cellular changes								
	Inclusion of glia				+	+		+	+
	Neuronophagic phenomenon				+	+			
	Disappearance of nerve cells surrounding small vessels								
	Pigmentary deposit								
	Severe changes				+	+			
Myelin sheath	Thinning of superficial fibers				+	+		+	
	Demyelination					+			
	Nodullar and tumor-like swelling				+	+			
	No changes								

Table 7. Changes in the motor and frontal areas.

	Epileptic brain	In chronic C.L.A. rabbit brains							
		4 times diluted solution					6 times diluted solution		Original solution
		3rd month	4th month	5th month	8th month	10th month	5th month	9th month	2nd month
Glia	Marginal gliosis ···	+	+	+	+	+	+	+	+
	Diffuse gliosis ···	+	+	+	+	+	+	+	+
	Gliosis in myelin ···	+	+	+	+	+	+	+	+
	Perivascular gliosis					+			
	Increase of glia surrounding nerve cells ··· ··· ···	+	+	+	+	+	+	+	+
	Increase of cells ···	+	+	+	+	+	+	+	+
	Increase of fibers ···			+	+	+		+	+
Vessels	Hypertrophy of wall					+			+
	Hyperemia and stagnation ··· ···								+
	Increase of cells into the wall ···					+			+
	Infiltration of leucocytes surrounding vessels··· ··· ···								
	Enlargement of lymphatic cavity in the mantel ··· ···				+	+		+	+
	Pigmental deposit in the wall cell ···								
	Infiltrating hemorrhage ··· ··· ···								
	No changes ··· ···								

Table 8. Changes in nucleus lenticularis.

Epileptic brain	In chronic C.L.A. rabbit brains							
	4 times diluted solution					6 times diluted solution		Original solution
	3rd month	4th month	5th month	8th month	10th month	5th month	9th month	2nd month
Young type of large nerve cells··· ···				+	+			

Nerve cells	Atrophy				+	+			
	Disappearance				+	+		+	+
	Dissolving changes			+	+	+		+	+
	Inclusion of glia				+	+		+	+
	No changes								
Myelin sheath	Demyelination								
	Laceration					+			
	Tumor-like swelling					+			
	No changes								
Glia	Increase of cells	+	+	+	+	+	+	+	+
	Increase of fibers				+	+		+	+
	No changes								
Vessels	Hyperemia and stagnation								
	Hypertrophy of wall					+			+
	Infiltration of leucocytes into the wall								
	No changes								

Table 9. Changes in substantia nigra.

	Epileptic brain	In chronic C.L.A. rabbit brains							
		4 times diluted solution					6 times diluted solution		Original solution
		3rd month	4th month	5th month	8th month	10th month	5th month	9th month	2nd month
Nerve cells	Atrophy				+	+			
	Disappearance				+	+			
	Dechromatisation								
	Vacuolar changes				+	+			
	No changes								
Myelin sheath	Demyelination								
	Laceration								
	Tumor-like swelling					+			
	No changes								

Glia	Increase of cells ···			+	+	+		+	+
	Increase of fibers ···				+	+		+	
	No changes ··· ···								
Vessels	Stagnation ··· ···								
	Small hemorrage ···								
	Hypertrophy of wall								+
	Infiltration of leucocytes into the wall								
	No changes ··· ···								

Table 10. Changes in cornu ammonis.

	Epileptic brain	In chronic C.L.A. rabbit brains							
		4 times diluted solution					6 times diluted solution		Original solution
		3rd month	4th month	5th month	8th month	10th month	5th month	9th month	2nd month
Nerve cells	Disappearance ···			+	+	+		+	+
	Disturbance of arrangement ··· ···			+	+	+		+	+
	Atrophy ··· ··· ···				+	+			
	Vacuolar changes ···				+	+		+	
	Cellular changes ···								
	Ischemic changes ···								
	Dissolving changes				+	+		+	+
	Edematous changes			+	+	+		+	+
	Severe changes ···				+	+			
	Neuronophagic phenomenon ··· ···								
	Pigmentary deposit								
	No changes ··· ···								
Myelin sheath	Demyelination ···				+	+		+	+
	No changes ··· ···								
Glia	Increase of cells ···	+	+	+	+	+	+	+	+
	Increase of fibers ···		+	+	+	+		+	+
	No changes ··· ···								

Vessels	Reproduction ··· ···				+			
	Enlargement of lymphatic cavity in the mantel ··· ···			+	+		+	+
	No changes ···							

Table 11. Change in the pia.

Epileptic brain	In chronic C.L.A. rabbit brains							
	4 times diluted solution					6 times diluted solution		Original solution
	3rd month	4th month	5th month	8th month	10th month	5th month	9th month	2nd month
Increase of connective tissue ··· ···								+
Hypertrophy ··· ···								+
Hyperemia ··· ···								+
Edema ··· ··· ···								+
Hypertrophy of vascular wall ··· ···					+			+
Vascular stagnation								+
Infiltration of leucocytes surrounding vessels ··· ··· ···								+
No changes ··· ···								

Furthermore, inclusion of glia, neuronophagy, tigrolysis, vacuolar degeneration of nerve cells and enlargement of *Virchow Robin*'s cavity were seen. Thus, we were able to reproduce the findings as seen in idiopathic epileptics. The difference between the two, is that, gliosis seen in idiopathic epilepsy is mainly the increase of macroglia, but in our case it was mainly the increase of microglia cells, though there was also a slight increase of macroglia. The other is, in idiopathic epilepsy disappearance of nerve cells are seen around small vessels in the cortex circumscriptly, while in our case it disappears in a generalized form.

I think this finding is the result of frequent attacks, and it is proper to think that rabbits which have not convulsed should appear as seen in our results.

13. Clinical experiences.

Of 147 in-patients, 97 were idiopathic epileptics and their histo-

ries tell that so-called allergic diseases, such as bronchial asthma, rheumatism and others were much fewer than expected. While there was considerably many so-called local infectious diseases such as otitis media, angina, sinuitis and teeth diseases and so fors. It seems as if these allergic diseases caused by focal infection have a significant meaning to idiopathic epilepsy.

Summary

In such animals not having any organic changes in their brains during the initial stage showed a descendence of convulsive threshold, abnormal findings in their electroencephalogram and ascending activity of ChE. But what is the cause of these functional changes? First, from the fact that though there was no organic changes, they were sensitized and reinjected by a known antigen, which is obviously an antigen-antibody reaction. Second, from the fact that we got a histological change, which was acknowledged as C.L.A. changes by increasing the concentration of these solution and the number of injections, it could be thought that these functional changes were caused by what I called latent C.L.A.. That is, it seems it could be thought that it would give functionally a permanent hypersensitivity, which is called convulsive arrangement. Furthermore, a similar histological findings as seen in old epileptics were made experimentally after prolonged and repeated injections of very diluted antigens. I believe it can be said, also from this histological point that they are experimental epileptics. But I am not trying to say that idiopathic epilepsy is the same allergic disease as asthma. If it was so, it should offer clinically a problem of eosinophilia in the blood of epileptics. But actually there is no eosinophilia in epileptics. Also, in adult epileptics, convulsive attacks is not often seen soon after introduction of antigens. Consequently, my theory that epilepsy is allergic, does not mean that allergy is the direct cause of epileptic attacks. What I mean is, the causal genesis of idiopathic epilepsy is hypersensitivity of nerve cells in the brain. This hypersensitivity was attained as a tissue reaction by some allergic mechanism without any organic changes. This functional change gives the nerve cell a hypersensitive state, which becomes the base of the beginning of convulsion. Its inducement of attack could be water stagnation in

the body, anemic state of the brain, alkalosis, or introduction of allergens. In short, the cause of attack does not always come from allergic reactions.

Conclusion

This study is still in progress and I cannot say that our experimental epilepsy is absolutely the same idiopathic epilepsy. To make the same one, it must have spontaneous attacks, which is the most important symptom. Very rarely I have seen those which showed spontaneous one, but these animals were under the influence of cardiazol. It is still not clear if I could make the same epilepsy in other animals as seen in human, whose cerebral cortex is highly developed. But I hope I will be able to make a nearest complete experimental epilepsy.

This article is an abstract of the following literatures from my department.

Sakakibara, J. Okayama med. assoc., OKAYAMA-IGAKKAI-ZASSHI, 64; 3, 347 (1952). Acta Med. Okayama, Vol. 8, No. 4. — *Kasai*, J. Okayama med. assoc., OKAYAMA-IGAKKAI-ZASSHI, 64; 8, 1587 (1952). Acta Med. Okayama, Vol. 8, No. 4. — *Oki*, J. Okayama med. assoc., OKAYAMA-IGAKKAI-ZASSHI, 64; 8, 1625 (1952). Acta Med. Okayama, Vol. 8, No. 4. — *Inoue*, J. Okayama med. assoc., OKAYAMA-IGAKKAI-ZASSHI, 64; 8, 1637 (1952). Acta Med. Okayama, Vol. 8, No. 4. — *Nishimoto*, J. Okayama med. assoc., OKAYAMA-IGAKKAI-ZASSHI, 65; 8, 1127 (1953). Acta Med. Okayama, Vol. 8, No. 4. — *Shimizu*, J. Okayama med. assoc., OKAYAMA-IGAKKAI-ZASSHI, 65; 8, 1153 (1953). Acta Med. Okayama, Vol. 8, No. 4. — *Kanematsu*, J. Okayama med. assoc., OKAYAMA-IGAKKAI-ZASSHI, 65; 8, 1256 (1953). Acta Med. Okayama, Vol. 8, No. 4. — *Tachibana*, J. Okayama med. assoc., OKAYAMA-IGAKKAI-ZASSHI, 65; 9, 1361 (1953). Acta Med. Okayama, Vol. 8, No. 4.

Literature

Gibbs, *Gibbs* and *Lennox*, Arch. Neurol. and Psychiat. (Am.), 50; 111 (1943). — *Katsura*, NIPPON-GEKA-GAKKAI-ZASSHI, 49; 174 (1948). — *Spratling*, cited from Practice of Allergy by Vaughan, 1948. — *Pagniez* and *Lieutaud*, Présse méd., 27; 693 (1919). — *Ward*, cited from Practice of Allergy by Vaughan, 1948. — *Howell*, cited from Allergy by Urbach and Gottlieb, 1946. — *Wallis*, *Nicol* and *Craig*, Lancet, 1; 741 (1923). — *McCready* and *Ray*, cited

from Practice of Allergy by Vaughan, 1948. — *Ball*, Amer. J. med. Sc., 173; 781 (1927). — *Rowe* and *Richet*, J. med. franc., 19; 170 (1930). — *Wilmer* and *Miller*, J. Allergy, 5; 628 (1934). — *Forman*, Arch. Neurol. and Psychiat. (Am.), 32; 517 (1934). — *Ealyeat*, cited from Allergy by Urbach and Gottlieb, 1946. — *Winkelmann* and *Moore*, cited from Allergy by Urbach and Gottlieb, 1946. — *Ward* and *Patterson*, Arch. Neurol. and Psychiat. (Am.), 17; 427 (1927). — *Beauchemin*, Amer. J. Psychiat., 92; 1191 (1936). — *Buchanan*, cited from Allergy by Urbach and Gottlieb, 1946. — *Ely*, Arch. Neurol. and Psychiat. (Am.), 24; 943 (1930). — *Stiefler*, Dtsch. Z. Nervenh., 81; 110 (1924). — *Spangler*, J. Lab. and Clin. Med., 13; 41 (1927). — *Adamson* and *Sellers*, J. Allergy, 4; 315 (1933). — *Clarke*, cited from Allergy by Urbach and Gottlieb, 1946. — *Vaughan*, Practice of Allergy, 1948. — *Rosenow*, Postgrad. Med., 2; 346 (1947). — *Bering*, J. Neurol. Neurosurg. and Psychiat. (Brit.), 14; 205 (1951). — *Jinnai*, NIPPON-RINSHO, 9, 1121 (1951). — *Davidoff*, *Kopeloff* and *Kopeloff*, J. Lab. and Clin. Med., 20; 1238 (1935). — *Davidoff*, *Seegal* and *Seegal*, J. exper. Med. (Am.), 55; 163 (1932). — *Davidoff* and *Kopeloff*, Proc. Soc. exper. Biol. and Med., 29; 71 (1931). — *Tokushige*, OKAYAMA-IGAKKAI-ZASSHI, 49; 2197 (1937). — *Miyahara*, SEISHIN-SHINKEIGAKU-ZASSHI, 42; 679 (1938). — *Nakanishi*, SEISHIN-SHINKEIGAKU-ZASSHI, 43; 297 (1939). — *Akamatsu*, NO-TO-SHINKEI, 1; 33 (1949). — *Iwasa*, NIPPON-GEKA-GAKKAI-ZASSHI, 53; 175, 216 (1952). — *Maekawa*, Report of symposium of hematology, 1; 203 (1947). — *Sawami*, SEISHIN-SHINKEIGAKU-ZASSHI, 53; 79 (1950). — *Rivers*, *Sprunt* and *Berry*, J. exper. Med. (Am.), 58; 39 (1933). — *Rivers* and *Schwentker*, J. exper. Med. (Am.), 61; 689 (1935). — *Freund* and *McDermott*, Proc. Soc. exper. Biol. and Med., 49; 548 (1942). — *Pacella*, *Kopeloff*, *Barrera* and *Kopeloff*, Arch. Neurol. (Am.), 52; 189 (1944). — *Morrison*, Arch. Neurol. (Am.), 58; 391 (1947). — *Cazzullo* and *Pacella*, Arch Neurol. (Am.), 63; 125 (1950). — *Pope*, *Morris*, *Jasper*, *Elliott* and *Penfield*, Epilepsy (Research in Nervous and Mental Disease, Vol. 26), 218 (1947). — *Inoue*, NO-TO-SHINKEI, 3; 215 (1951). — *Elliott* and *Penfield*, J. Neurophysiol., 11; 485 (1948). — *Inoue*, NO-TO-SHINKEI, 2; 111 (1950). — *Campbell*, *Alexander* and *Putnam*, Arch. Neur. (Am.), 39; 1150 (1938). — *Wake*, BYORIGAKU-ZASSHI, 1; 219 (1942). — *Scholz*, Z. Neur., 164; 117 (1939). — *Hamazaki*, NIPPON-BYORI-GAKKAI-ZASSHI, 24; 91 (1934).