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Kiyoshi Hiraki* Yoshikatsu demiya†

Hiroshi Kageyama‡

*Okayama University,

†Okayama University,

‡Okayama University,

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Kiyoshi Hiraki, Yoshikatsu demiya, and Hiroshi Kageyama

Abstract

1. In application of ACTH on seven cases, we obtained dramatic effects on all of them this summer (1957). 2. We believe that the mechamism of ACTH actions are responsible to the diminution of inflammatory reactions in the brain. 3. We are now conducting a series of experiments with the use of animals, the results of which will be reported later.

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THE THERAPEUTIC EFFECTS OF ACTH ON JAPANESE B ENCEPHALITIS

Kiyoshi HIRAKI and Yoshikatsu DEMIYA and Hiroshi KAGEYAMA

Department of Internal Medicine, Okayama University Medical School Okayama, Japan (Director : Prof. Kiyoshi Hiraki)

Atsumaro KIYAMA

Okayama City Hospital, Okayama, Japan

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Despite strenuous and unceasing efforts by so many investigators in the battle against the diseases caused by viruses of medium or small size, no effective agents have yet been found for such diseases, and in this respect the same holds true with Japanese B encephalitis.

However, if we list the names of drugs commonly employed in the treatment of Japanese B encephalitis in our country, such as X-ray, autohormone, osone, immune horse serum, sulfanilamide and its derivatives, convalscent's serum, lumbal administration of thiamine, high amount of thiamine, urotropin, phenosulfazole, para-aminobenzoic acid, sulfamerazine, penicillin, and glucose solution in high concentration (by carotic arterial injection), aureomycine, sodium phenylazonaphionate, terramycine, protamide, silver-sol, streptomycine, stibunal agents, γ-globuline, and O. B. S. T. (Oxybenzolsulfaminothiazole), cortisone, pans 610-Tw and P^{32}. Of them, we have been mainly using both clinically and experimentally such agents as immune horse serum, various sulfamine derivatives, human serum in convalescent stage, thiamine, various antibiotics and panses, but all in vain. Venturing to pick one that would prove to be of any use, we may point out radioactive P^{32} which has been found experimentally to prolong somewhat the length of incubation period as well as the period of time to death, as shown in previous report[5]. From this view-point, we had hoped to use this P^{32} clinically in this summer when Japanese B encephaplitis is usually prevalent but due to the difficulty in obtaining this substance as well as its shortness of half value period, we missed the chance of utilizing this isotope P^{32} clinically.

This summer we have employed ACTH for the treatment of

Table 1. Principal Neurologic Symptom at Admission

Patients	M. H.	M. N.	Y. Y.	I. M.	T. K.	K. S.
Symptoms	32, ♂	6, ♀	5, ♂	2, ♀	5, ♀	8, ♀
Disturbance of consciousness	(卅)	(卅)	(卅)	(卄)	(卄)	(+)
Pupillary width	normal	miesis	mydriasis	normal	normal	normal
Light reflex	normal	normal	delayed	normal	delayed	delayed
Muscular rigidity	(+)	(+)	(−)	(+)	(+)	(−)
Involuntary movement	(+)	(−)	(−)	(−)	(−)	(−)
Stiff neck	(卄)	(卄)	(+)	(卄)	(卄)	(+)
Kernig's sign	(卄)	(卄)	(+)	(+)	(+)	(±)
Tendon reflex	decreased	decreased	decreased	increased	lost	decreased
Skin reflex	lost	lost	lost	normal	lost	normal
Pathologic reflex	(−)	Babinsky (±)	(−)	(−)	(−)	(−)
Clonus	(−)	(−)	(−)	(−)	(−)	(−)
Tonic spasm	(−)	(−)	(+)	(+)	(−)	(−)
Clonic spasm	(−)	(+)	(+)	(−)	(−)	(−)
Disturbance of sensitivity	(+)	(−)	(+)	(−)	(−)	(−)
Bladder-rectum disturbance	urino retention	incont. urine	incont. urine	incont. urine	incont. urine	incont. urine
apearance	clear Sonnenstäubchen	slightly turbid	clear Sonnenstäubchen	clear	bloody by technical error	bloody by technical error
pressure	220	270 160	400	300	160 100	150 80
cell-count per c. mm.	382/3	452/3	1136/3	1447/3	90/3	549/3
Liquor Nonne-Apelt	(+)	(+)	(+)		(+)	(+)
Pandy	(卄)	(+)	(+)	(+)	(+)	(+)
M. N.-reaction	encephalitic type	indefinite	encephalitic type		encephalitic type	
Sano's reaction	(卄)	(+)	(卅)	( )	(−)	(+)

Table 2. Application of ACTH

Patient	Sex	Age	Weight	Initial daily dosage	Time for pyretorytic effect	Method	Total doses	Length of time	Side effects
M. H.	♂	32	52.0 kg	0.8 mg/k	12	ACTH Gel intra-muscular injection four times a day	250 mg	7 days	Slight palpebral edema
M. N.	♀	6	17.0	1.2	24	ACTH Gel intra-muscular injection once a day	66	4	Arhythmia facial edema
Y. Y.	♂	5	15.5	1.3	24	〃	71	5	
I. M.	♀	2	8.4	1.2	24	〃	28	3	Slight facial edema
T. K.	♀	5	14.5	1.4	9	〃	50	6	
K. S.	♀	8	20.5	1.0	20	〃	55	6	Slight facial edema

Japanese B encephalitis and being able to obtain dramatical results, we make case report here with the hope that general practitioners may avail themselves of the efficacy of these agents.

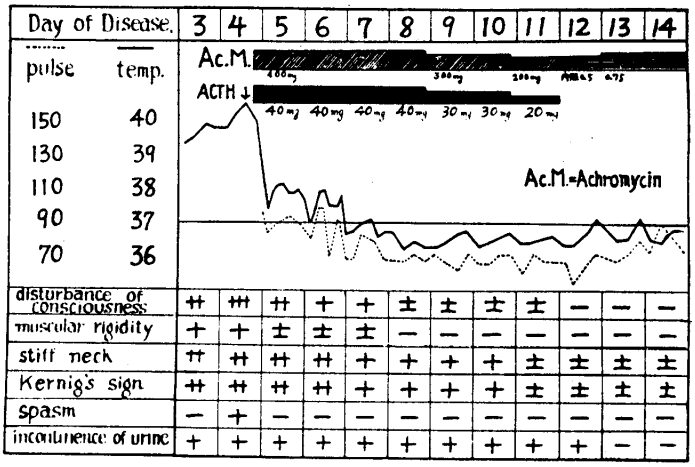
CASE REPORT

We will describe only one case somewhat in detail (as for Cases 2—7, see figures and tables)

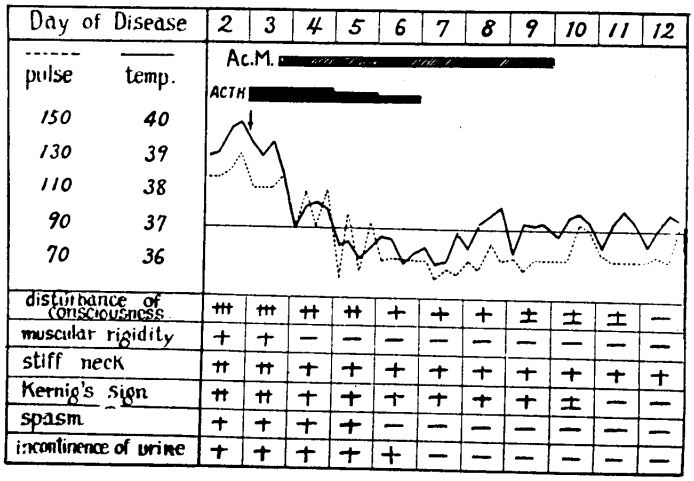
Case 1. M. K., a 31-year-old male clerk; chief complaints were high temperature and losing consciousness. He was hospitalized for one month in 1947 for stomach ulcer. Had hepatitis in 1956. Family history revealed a maternal grandmother died of Japanese B encephalitis after recession of fever at the age of 75 years. His elder sister died of acute poliomyelitis when she was only 7 years old.

History prior to the addmission. Although he felt tired, he had worked at his office as usual up to September 2, 1957. He began to complain of headache with temperature at 38°C on Sept. 3, 1957 (the first day of illness) and the temperature rising steadily, he had lost appetite and went to bed. On Sept. 4 his headache became severe with temperature at 38.4°C. He then consulted with a physician and received some medicine, but his temperature kept on rising, accompanied with vomiting. His vomiting became frequent and he vomited something like bile. On Sept. 5 (the third day of illness), his headache became still more severe and

Case 1. M. H., Age 35, Sex Male

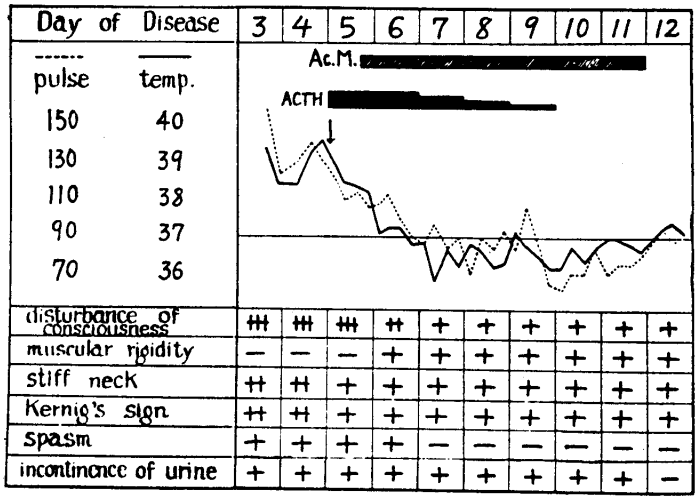


Case 2. M. N., Age 6, Female

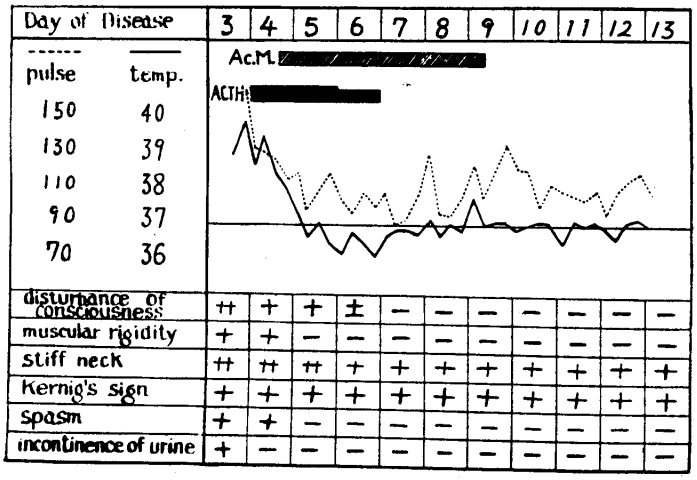


called for a doctor who advised him to take chloramphenicol. Even after the total of three administrations of chloramphenicol no improvement was observed. At 3 p. m. his temperature was 39.6°C, and at 6 p. m. 39.9°C, and in the evening his consciousness became hazy. He was again examined by a physician who found stiff neck and trismus; and the patient began to have lingual delirium. These symptoms being suggestive of Japanese B encephalitis, he was advised to be hospitalized. He began to floccilate with right hand on that night. Losing consciousness on Sept. 6 (the fourth day of illness), the movement of his limbs grew violent, and

Case 3. Y. Y., Age 5, Male



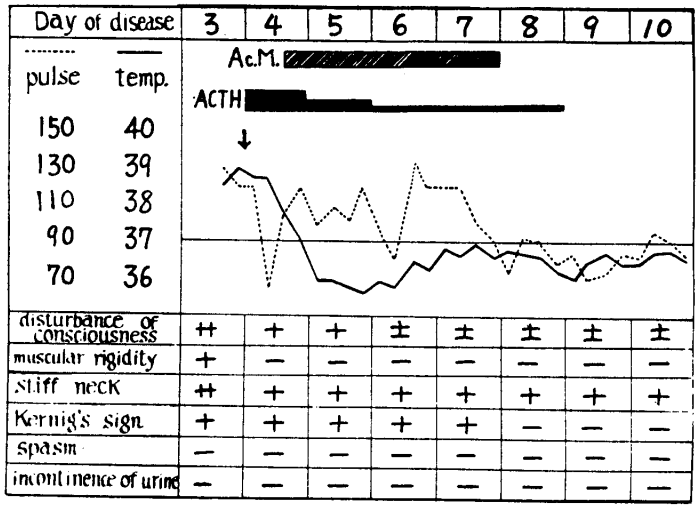
Case 4. I. M., Age 4, Female



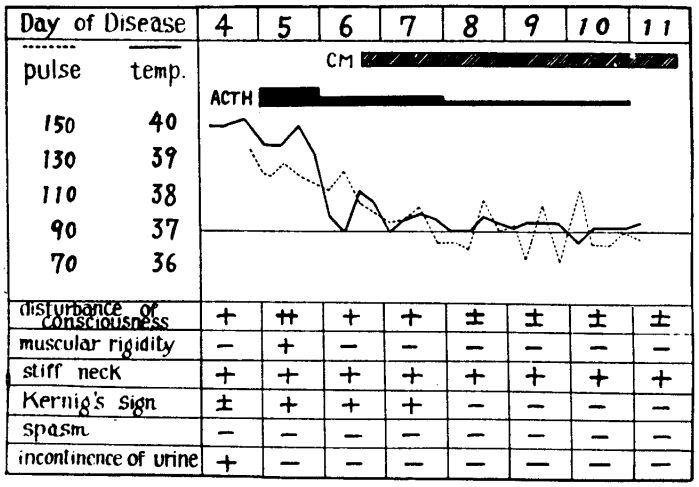
his temperature reaching as high as 40.5°C, he fell into coma. He was admitted to the Hiraki Clinic of Internal Medicine at two p. m. on the same day.

Findings at the admission : In the state of coma with no response to questions asked, he continued to floccilate with right hand. His face expressionless ; pulse 100 per minute, regular, tension good ; temperature, 40.1°C ; slight miosis ; pupillary reflex normal, palpebral and bulbar conjunctiva somewhat congested ; the tongue with a thick white coating ;

Case 5. T. K., Age 5, Female



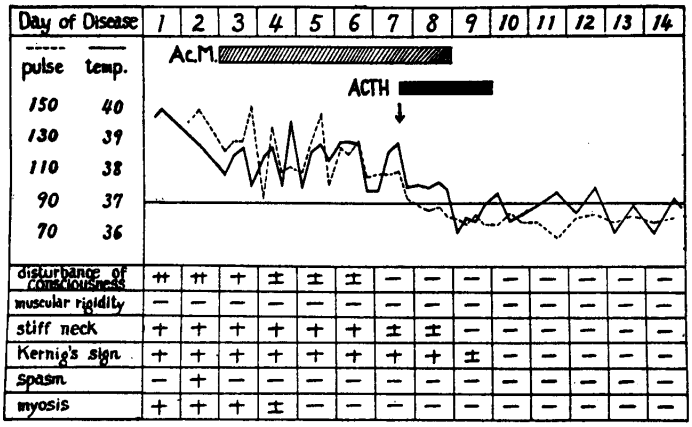
Case 6. K. S., Age 8, Female



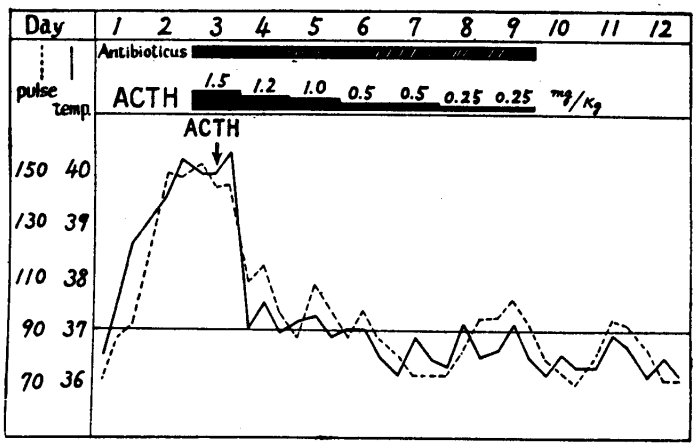
reddening of pharynx; the size of the heart, normal; heart sound, frequent but clear; the lung showed hardly any physical changes; in the abdomen, the liver and spleen, not palpable; knee jerk but ankle jerk on both sides, normal; Babinsky test (−); Oppenheim reflex (−); ankle-clonus(−); patellar-clonus(−); abdominal reflex, lost; cremasteric reflex, lost; stiff neck; Kernig's sign; rigidity of hands and legs, positive (right hand is stiffer than left hand)

Results of examinations : Cerebrospinal fluid was watery, but

Case 7. K. M., Age 7, Male



Standard of ACTH Treatment for Japanese B Encephalitis



lightly murky (Sonnestäubchen); no xanthochrome; initial pressure, 220 mm. H_2O; 5 cc. aspirated; terminal pressure could not be measured because of violent movement of the patient; Nonne-Apelt reaction (+); M-reaction (+): N-reaction (±); Sano's reaction (++); cell count, 382/3 per cubic millimeter.

Urine was brownish, transparent, and acidic; its specific gravity 1,030; protein in sulfo-salicylic-acid test (++) and in heat-and-acid test (+); sugar (+); urobilinogen test (+++) urobilin test (±); indican test (−); acetone test (−) diazo reaction (−); in precipitation erythrocytes (−), leucocytes 3—4/v. f.; epithelial cells, 1/v. f.; urinary cast, none; bacilli, not present; no abnormality in the liver function tests; blood

tests for syphilis, negative ; and the blood picture revealed : Hb 90% ; erythrocyte count, 482×10^4 ; leucocyte count, 11,100 ; hemoglobin index, 0.93 ; and leucocyte percentage revealed, no mononuclear neutro phils ; polymorphs 74.5% ; while large lymphocytes, 1.0% ; small lym phocytes, 16.0% ; monocytes, 8.0% ; eosihophils, none, and no baso-philocytes.

The progress of illness ; On admitting him into our clinic at 2 p. m. on Sept. 6, 1957, he was given cardiotonics, and from 4 : 30 p. m. he was put on ACTH-gel treatment (on the dosage of 40 mg. per day divided into 4), and in addition, achromycine injections were started from 6 p. m. It had not been possible to perform lumbar puncture due to violent move-ments but after the second injection of ACTH-gel, the puncture was poss-ible as he quieted down a little. Even then he remained unconscious but his temperature fell to 38.7°C at 12 p. m. On Sept. 7 (the fifth day of illness) at 2 a. m. it came down to 38°C and at 6 a. m. to 37.4°C and in the meantime the patient began to respond more to the pain of injection, but even then he kept up his violent movement during catheterization. Moreover, although he still kept on trying to get up unconsciously or kept up floccilation, on the whole, he became quieter than the day before. At around 10 a.m. he began to respond by nodding when his name was called, and he started to make effort to open his mouth when he was asked to, but he again relapsed into soporous state. At 11 a. m. the temperature fell to 37.9°C and his responses grew stronger and he even began to make effort to talk. At 1 p. m. his temperature was 38.3°C while at 3 p. m. it was 37.9°C and at 5 p.m. the patient became more responsive ; and abdo-minal reflex appeared on the upper part of abdomen at the same time, a slight cremasteric reflex showed itself on the right side. At 11 : 30 p. m. at the time of catheterization he uttered a few words, "That is enough", or "Don't say it so often", but he was still in the soporous state.

On Sept. 8th (the sixth day of illness) his violent action almost sub-sided, and though he was in somnolescent state and had lost his orientation, he became fairly responsive to a stimulation and his word in talk grew cle-arer ; no abdominal reflex on the either side of lower abdomen ; cremasteric reflex, on the right (+), on the left (±) ; appetite returned ; when food such as 380 cc. of fresh milk, the yolk of an egg, 120 cc. of apple juice, and 20cc. of tea had been given through a nasal tube, he uttered "I don't like it through the nose", or "I cannot taste it." etc. At 5 : 0 0 p. m. when he was again fed through the nasal tube, his utterances became still clearer. Although he had retrograde amnesia, he could recall things far in the past. About this time he began to have good appetite. Difficulty

of swallowing disappeared almost completely ; mascular rigidity (+) ; Kernig's sign (++) ; stiff neck (++) and he hardly complained of headache. Under such conditions, he gradually regained his consciousness.

Sept. 9 (the seventh day of illness) ; the temperature returned quite normal. Sept. 10 (The eighth day of illness) he regained consciousness quite completely (after total injection of 170 mg. of ACTH-gel). There still remained stiff neck (+), Kernig's sign (+), and muscular rigidity (±) but the muscular rigidity disappeared on Sept. 13 (the eleventh day of illness). Moreover, retension of urine persisted up to Sept. 14 (the twelfth day of illness), but stiff neck and Kernig's sign became gradually negative on Sept. 18 (the 16th day of illness).

The findings on the cerebrospinal fluid : The fluid was quite watery transparent, no Xanthochrome ; the initial pressure, 120 mm. H_2O; after 10 cc aspiration the pressure fell down to 70 mm. H_2O ; Nonne-Apelt reaction (+), and cell count, 148/3 per cubic millimeter. He was discharged in the evening of Sept. 19 (the 17th day from the onset of disease).

Thereafter, he is recovering favorably without any notable sign of relapse.

DISCUSSION

It is the concensus of opinions that the inoculation of virus into the animals previously administered with hormones such as ACTH and cortisone aggravates the symptoms. In spite of this fact, the reasons why we used these hormones in the treatment of Japanese B encephalitis lie in the following :

1) As stated by MINOBE[1], hormones such as ACTH and cortisone, have come to be used extensively in the various fields of medicine and present many interesting findings in the application of such hormones, especially in the critical moment of extremely acute cases. Even in the cases where the mechanism is often indistinct, the application of these hormones for saving life of acute diseases is steadily gaining its usefulness. Recently with the use of ACTH to a narcotic poisoning case who had fallen into coma with high temperature, being on the verge of death, and to a patient suffering from Basedow disease, who had developed severe hepatitis and fallen into hepatic coma, we have been able to obtain dramatic effects.

2) ACTH and cortisone possess inhibitory power against inflammatory tissue reactions, namely, the inhibitory actions on the exudative mechanism, capillary hemorrhages, and edemas. In other words, in the

case of Japanese B encephalitis in which the central nervous system undergoes extensive pathologic changes, even if these medicaments do not have killing power against the virus, as claimed by RUSSEK[2], when the tissue reactions are diminished, nerve cells apparently on the verge of death due to anoxia will naturally be revived and the irreversible changes in the brain will very likely be held at minimum, at the same time it is predictable that antipyretic effects of these agents will markedly lessen the danger of death from Japanese B encephalitis which is specifically accompanied by high temperature.

3) Japanese B encepalitis is an infectious disease which progresses rapidly with acute high temperature and the death of patient often occurs on the fifth to the seventh day after its onset. If the crisis is overcome by some means, this disease can be cured with relatively little sequel.

4) Although Japanese B encephalitis is neurotropic in nature, it is also somatic ; namely, it passes through the so-called visceral stage then into the cerebrospinal stage. It also is generally known that extensive pathologic changes occur in various organs, and consequently, a diminution in the functions of the pituitary body and of the adrenal cortex.

5) In the application of ACTH and cortisone, if the dosage is not in excess and the length of time applied is short, the side effect will be only slight edemas, and even such side effect will soon disappear on the cessasion of the treatment and no serious side effects can be thought to occur.

Furthermore, it seems more appropriate to use some hormones belonging to the cortisone group rather than ACTH in the treatment of this disease in which are recognized histo-pathological changes not only in the pituitary body but also in the adrenal cortex, but ACTH is thought to possess a pathway not solely through the adrenal cortex but also some unknown mechanism by which it is thought to act effectively and directly on the central nervous system. For this reason, we employed ACTH first of all in our clinic this summer (1957).

Thus, in our application of ACTH for severe cases of Japanese B encephalitis, the results turned out to be far more satisfactory than expected. It has proved that if the amount of ACTH is adequate the antipyretic effect is observable within several hours after its administration; and within 24 hours the temperature falls down to around 37°C and at the same time the pulses decrease proportionately to the fall in temperature, and the tension of the radial artery wall is strengthened, the disturbance of consciousness as well as muscular rigidity begin to recede and consequently the patient will become quieter and begins to have a good appetite. From our experiences, it has been found that the symptoms most difficult

to receive the beneficial effect of ACTH are meningeal signs such as stiff neck and Kernig's sign.

In any event, the conditions of these patients improve somatically after the administration of ACTH to such a dramatic extent that the turn for the better gives comfort and hope not only to the families of the patient but also to the physician in charge. If we boldly draw a standard of the ACTH treatment from our seven cases, it may be started at first with 1.5 mg./kg. a day, and gradually decreasing the amount, the treatment is to be ceased in one week, as shown in figure, but as a precautional measure against a possible secondary infection such as pneumonia, it will be advisable to use some antibiotics concurrently.

Now, reviewing the available literature concerning ACTH and cortisone, we can find only the articles by KUDO[3] and AIZAWA[4] on the therapeutic uses of these agents. Namely, KUDO *et al*[3]., in the report on the effects of ACTH against the functions of the adrenal cortex in the treatment of Japanese B encephalitis delivered at the General Meeting of the Japanese Association for Infectious Diseases, recognized disturbances in the adrenal cortex of the patient suffering from this disease with Thorn's test and stated that ACTH will offer some benefitial effects. They went on further that from their animal experiments ACTH seemed to possess no killing action against the virus ; while AIZAWA[4], in his application of cortisone therapy on one case of Japanese B encephalitis encountered in the summer last year, described that he was impressed by the fact that cortisone had striking effects on the muscular rigidity or on spasticity and on the disturbances of consciousness, but he did not mention anything about the antipyretic effects which proved to be the most remarkable in our own experiences.

Be as it may, we have undertaken first of all ACTH treatment for seven cases of Japanese B encephalitis this summer (1957) on the basis of reasonings mentioned above, and having successfully obtained dramatic effects on all the seven cases, we have been able to establish our own standard of ACTH treatment. We wish that various investigators will try this treatment and wish to receive unbiased criticism on this subject.

It is earnestly hoped that the menace of Japanese B encephalitis, which rampages year after year during hot summer days as it were a routine annual round, possessing a high mortality rate (30—40%) be minimized even to a slight degree with the use of ACTH.

At the present, we are conducting a series of investigations on various effects of ACTH and cortisone against experimental Japanese B encephalitis with the use of monkey and mice, and the results of which are

to be reported in near future.

SUMMARY

1. In application of ACTH on seven cases, we obtained dramatic effects on all of them this summer (1957).

2. We believe that the mechamism of ACTH actions are responsible to the diminution of inflammatory reactions in the brain.

3. We are now conducting a series of experiments with the use of animals, the results of which will be reported later.

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