STUDIES ON "KASEN" OF HORSES IN HOKKAIDO VI.

THERAPEUTIC SIGNIFICANCE OF ANTIHISTAMINE PREPARATIONS FOR HORSES AFFECTED WITH THE DISEASE

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INTRODUCTION

On the basis of results obtained from the writers' several years' investigations, "kasen" was thought to be an allergic disease caused by the hypersensitivity to the bites of some bloodsucking insects. Therefore, authors conducted preliminary experimental treatment for 32 horses affected with the disease by injections of antihistamine preparations and spray of insecticides in the summers of 1955 and 1956. When the patients were treated with antihistamine preparations alone, the itchiness reappered in several days after the injections. However, when the insecticides were sprayed sufficiently in parallel with the injections and furthermore when they were used continuously for a longer period, no relapses were found. The characteristic findings, in the course of the experiment, were the gradual decrease in eosinophile numbers and in histamine concentrations after the injections; the variations in both constituents ran almost parallel with that of the clinical syndromes.

Field experiments were conducted again on 44 affected horses in the summer of 1957 to check the above statements that the injection of antihistamine preparations and the spray of insecticides are beneficial for treating the disease. The results will be described in the present paper.

EXPERIMENTAL MATERIALS AND METHODS

General view of the experimental methods and results are indicated in table 1.

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1) Locality of experiment

The experiments were made on patients living in 4 districts of Hokkaido. The 1st district is Tokoro village of Kitami near the Okhotsk Sea; the field are level land or hillocky. The 2nd is Kotoni and 3rd is Tobetsu. The former has preponderance of paddy fields and the latter is hillocky. They are situated at a distance of 10 and 40 km from Sapporo respectively. The 4th is Shinshinotsu which is distant approximately 40 km from Sapporo. The farms are almost entirely paddy fields and near the Ishikari River. A common fact was found in the 4 districts that the majority of bloodsucking insects occurred in the summer; also the severity of itchiness of attacked horses was influenced by the occurrence of bloodsucking insects and by rise and fall in atmospheric temperature.

2) Experimental horses

Forty-four patients were employed for the experiment. They were 3 to 18 years old and all were well nourished. Hair color was almost black or black-brown and chestnut was found in a few cases. Almost all the horses were female mongrel Percheron; they were engaged in farm work in the daytime every day and were fed in stables at night. The ages of the animals as the initial attack of the disease, in most cases, were 2 to 6 years; the youngest of several months after birth and the oldest of 18 years were found respectively in small numbers. Since the patients had all been attacked by the disease in every summer, they had had 3 to 15 reoccurrences since birth, and the disease attacked only some limited horses.

The long hair areas in the tails and cervicals were usually attacked most seriously and next were those of short hair in the shoulder, hunch, back and rump. Lesions were found on the skin of the abdomen and mandible in very few cases. In general, scurfs were found in abundance in the cervical long hair regions in almost all cases. Papules and nodules were formed on the skin surface in the cases which were thought to be in the initial stage of the disease. In the skin of serious cases, remarkable dermatitis was noted, and shortening or falling off of the hair, swelling of the skin, ulcer and crust formation and elephant-like skin disease were noted respectively.

Ten non-affected horses were used as control for the purpose of comparing the clinical syndromes and the blood constituents with those of the affected animals.

3) Therapeutic medicines

Antihistamine preparations were used for the experiments; Allergin (chlorprophen-pyridamine maleate)*, Hiberna (promethazine hydrochloride)**, Pyribenzamin (benzyl-(α-pyrisill)-dimethylendiamine)*** and Venacalcium B_6 (diphenhydrochloride, bromcalcium and vitamin B_6).****

Spraying of DDT (5~10%) and BHC (1.5~3.0%) powders was conducted in parallel with the injections of the antihistamine preparations. They were mainly sprayed over the regions of long hair and the vicinity of the stables as it was done in the preceding year

* Manufactured by Sankyo Co., Ltd., Tokyo.
** Manufactured by Yoshitomi Pharmac. Co., Ltd., Osaka.
*** Manufactured by Takeda & Ciba Pharmac. Co., Ltd., Osaka.
**** Manufactured by Tanabe Pharmac. Co., Ltd., Osaka.

for the purpose of exterminating the bloodsucking insects.

4) Therapeutic methods

The medicines were injected in the period from the middle of July to late August. The conditions of the patients were most serious. The experimental horses were divided into 4 groups.

The 1st group consisted of 18 cases and Allergin was applied subcutaneously; 15 cases in Tokoro district and 3 cases in Kotoni district were injected in the amount of 200 and 300 mg per day for 5 days respectively. Insecticide applied in the former district was BHC and in the latter, DDT.

The 2nd group was comprised of 5 cases of Shinshinotsu. Hiberna was injected at the rate of 200 mg per day for 5 days intravenously and DDT was used.

The 3rd group consisted of 4 cases in Tobetsu and 3 cases in Kotoni. Pyribenzamin was injected in the amount of 200 or 300 mg per day for 5 days intravenously and DDT was applied to all cases.

The 4th group consisted of 14 cases; 5 cases in Kotoni, 3 cases in Tokoro and 6 cases in Shinshinotsu. They were all injected with Venacalcium B_6 in the amount of 200 or 300 mg per day for 5 days intravenously. BHC was sprayed for the patients in Tokoro, and DDT was used in the other 2 districts.

The observation periods after the injections were from 16 to 25 days and the spraying of insecticides was continued for a longer time in each locality.

5) Blood examinations

Counts of blood cells, classifications of leucocytes, measurements of serum protein, blood suger levels, serum inorganic phosphorus, serum calcium and plasma histamine concentrations were conducted respectively. For the biochemical analysis of blood constituents a photoelectric photometer was used; the method of measurement of histamine concentrations followed KOMAKI's modified from LUMBSCHEZ's method.

Results of Investigations

Out of 44 cases, 36 were decided to have shown complete healing and 6 cases relapsed. However, the conditions of 2 cases were unchangeable in comparison with the condition before treatment. A general view of the results is shown in table 1.

1. Clinical Findings

Inspections and palpations were performed for all cases in the course of the experiments.

1st group Eighteen patients were examined for injections of Allergin; insecticides used were BHC and DDT. The observation period after the injections was 16 or 25 days. In fourteen cases (77.7%) out of 18, complete recovery was found but the other cases (22.2%) relapsed. Generally on the 2nd and 4th days from the commencement of the experiment, decrease of itchiness occurred. When the treatment was ended, the itchiness of lesions disappeared and the conditions seemed to indicate recovery. Although in 4 out of 11 cases in Tokoro district, itchiness reappeared from the 3rd or from the 5th day

TABLE 1. *Therapeutic Methods and Results*

GROUP	MEDICINE	LOCALITY OF EXPERIMENT	NO. OF CASES	DOSE	INJECTION METHOD	INSECTICIDE	OBSERVATION PERIOD	RESULTS		
								Recovery	Relapse	No-change
I	Allergin	Tokoro	15	200 mg/day for 5 days	S.C.	BHC	16~25	11	4*	0
		Kotoni	3	300 mg/day for 5 days	S.C.	DDT	16	3	0	0
		Total	18					14 (77.7)	4 (22.2)	
II	Hiberna	Shinshinotsu	5	200 mg/day for 5 days	I.V.	DDT	19	5 (100)	0	0
III	Pyribenzamin	Tobetsu	4	200 mg/day for 5 days	"	"	16	2	1*	1*
		Kotoni	3	300 mg/day for 5 days	"	"	16	3	0	0
		Total	7					5 (71.4)	1	1
IV	Vena-calcium B_6	Kotoni	5	300 mg/day for 5 days	I.V.	DDT	16	5	0	0
		Tokoro	3	200 mg/day for 5 days	"	BHC	25	2	1*	0
		Shinshinotsu	6	250~300mg/day for 5 days	"	DDT	19	5	0	1*
		Total	14					12 (85.7)	1	1
Total			44					36 (81.8)	6 (13.7)	2 (4.5)

Note: *···Insecticides were not sprayed sufficiently.

after the termination of the treatment, reappearance of the itchiness, in the cases of Kotoni district, was not found.

Observing the results in the 14 recovered cases, the insecticides were used sufficiently even after the injections of Allergin were discontinued, so the lesions have taken a favorable turn. That is to say, regarding the changes of lesions in the skin, disappearance of itchiness, papules and nodules, softening of skin tissues, prolongation of hair, gradual healing of dermatitis and crust formations were observed respectively. The absorption of the drugs injected subcutaneously was not rapid but no other clinical disturbances were found.

2nd group Five cases were injected with Hiberna and sprayed with DDT. The observation period after the end of the injections lasted 19 days. All patients recovered completely and no relapses were observed. Since in this group, the attention of the owners was drawn to the matter of spraying insecticides, no cases of reappearance of itchiness were found. The process of the healing of the patients was almost identical with that of the cases in the 1st group.

3rd group Four cases in Tobetsu and 3 cases in Kotoni were used for Pyribenzamin treatment respectively and DDT was sprayed throughout the experiment. Observations after the injections were discontinued at 16 days. Five cases out of 7 (71.4%) recoverd completely, but in Tobetsu 1 case relapsed from 1 week after the injections and no change of conditions was found in one other case during the experiment.

With respect to defective 2 cases, the occurrence of bloodsucking insects in their stables was more prevalent than in other ones and further, insecticides were not sprayed at all by owners from beginning to end of the experiment; however, during the injections of antihistamine, there was found a decrease of itchiness to some extent. In the recovered cases, the course of recovery resembled that described above in the 1st group.

4th group In the 4th group, 14 cases were administered Venacalcium B_6 treatment. Their injection doses were 200~300 mg per day for 5 days intravenously. DDT was used for the cases in Kotoni and Shinshinotsu and BHC was sprayed for those of Tokoro. Clinical observations after the injections ended at 16 or 25 days.

As for the results of the experiments performed with above described methods, complete recovery was noted in 12 cases (85.7%), 1 case relapsed and the other 1 case showed no changes as compared with the pre-treatment conditions. The changes in the course of the treatments in recovery cases were similar to that of the lst group. The states of the one recovered case are shown in figs. 1~4.

2. Hematological Findings during the Experiments

The blood was examined morphologically and biochemically.

1) Morphological findings on blood cells.

The findings are indicated in table 2.

Non-treated group Firstly, as indicated in table 2, the authors compared the morphological states of blood between 10 affected and 35 non-affected horses for a full

TABLE 2. *Variation of Blood Cells in the Course of the Treatment*

	DIVISION	NO. OF CASES	TIME OF EXAMINATION	ERYTH. (mill.)	LEUC.	PERCENTAGE OF LEUCOCYTES					
						Rod.	Seg.	Ly.	Mon.	Eos.	Bas.
Non-tretaed Group	Healthy	10	Midsummer	7.24	8,680	1.1	45.4	48.3	1.9	3.0	0.3
	Patients	35		7.51	9,280	0.6	51.4	39.5	2.3	6.1	0.2
Treated Group	Allergin	11	Pre-injec.	9.03	11,300	1.8	44.9	42.9	3.2	7.0	0.2
			Just post-injec.	10.31	10,800	0.5	36.5	58.5	2.0	2.0	0.5
			7th day post-injec.	7.60	9,600	0.5	44.0	47.2	2.7	5.4	0.2
			14th day "	9.39	6,000	0.4	46.2	48.1	1.3	3.8	0.2
	Vena-calcium B_6	13	Pre-injec.	7.58	9,000	1.0	56.0	35.4	2.4	5.0	0.2
			Just post-injec.	7.08	8,900	0.5	46.5	47.8	1.7	3.1	0.4
			7th day post-injec.	6.66	8,500	0.7	35.8	59.9	1.0	2.5	0.1
			14th day "	7.35	8,800	0.5	42.2	51.7	1.8	3.6	0.2
	Hiberna	4	Pre-injec.	8.02	8,600	0.4	48.3	42.2	1.0	8.1	0
			Just post-injec.	7.88	9,000	1.5	39.2	52.0	2.7	3.9	0.7
			7th day post-injec.	6.40	7,100	0.2	38.5	58.3	1.2	1.8	0
			14th day "	6.77	10,100	1.1	48.1	47.3	1.1	1.8	0.6
	Pyribenzamin	3	Pre-injec.	6.83	8,200	0.3	52.5	39.5	2.2	5.5	0
			Just post-injec.	7.54	9,800	0.7	41.6	52.9	2.6	2.2	0
			7th day post-injec.	8.24	7,300	0.7	52.5	42.5	1.3	2.7	0.3
			14th day "	7.27	7,900	0.2	47.1	44.5	0.7	2.8	0.7
	Average	31	Pre-injec.	7.77	9,200	0.4	53.5	38.7	2.0	4.9	0.5
			Just post-injec.	7.56	9,400	0.7	42.8	51.4	1.9	2.8	0.4
			7th day post-injec.	6.99	8,200	0.7	37.5	58.2	1.3	2.0	0.2
			14th day "	7.59	8,500	0.6	42.1	52.4	1.3	3.3	0.3

summer. From the average values, erythrocytes were counted to 7.24 million in normal horses and 7.51 million in affected horses. Leucocytes showed 8,680 in the former and 9,280 in the latter. In differential counts of leucocytes, no great differences were shown in neutrophiles, lymphocytes, monocytes and basophiles. However, eosinophiles were counted to 3.0 per cent in the non-affected and to 6.1 per cent in the affected animals respectively. So the increase in eosinophile numbers is considered to be the most characteristic finding in the disease.

Treated group As was shown in table 2, blood examinations were performed on 31 treated horses; Allergin group 11, Hiberna group 4, Pyribenzamin group 3 and Venacalcium B_6 group 13. The blood was sampled 4 times; just before the injections, just at the end of the injections, 7 and 14 days after the injections. Taking a general view of the descriptions in each group, one becomes aware of variations of numbers in eosinophile leucocytes. The percentages of the cells averaged in each group just before the injections of medicines ranged from 5.0% to 8.1%. When the antihistamine preparations were injected for 5 days respectively, the number of the eosinophiles decreased to 2.0~3.9%. Namely, the eosinophile counts decreased to about one half or to one third. Then the cells had a tendency to sustain their values or to diminish in accordance with the spray of the insecticides; no cases regained the pre-investigation values. No other respects were remarkable changes observed.

2) Biochemical Findings on Blood

The findings are shown in table 3.

For the purpose of comparing the blood chemical states of non-treated horses with those of treated ones, biochemical analysis was conducted on 10 normal and 24 affected horses simultaneously with the morphological examinations during the entire summer.

Non-treated group In the analysis, as shown in table 3, characteristic results were found except in respect to histamine concentrations. Mean values of histamine contents indicated 1.14 γ/ml in normal horses and 3.89 γ/ml in affected horses respectively. Therefore, the histamine concentrations in the affected horses were above three times than that of the normal horses.

Treated group The analysis was conducted on 20 patients; Allergin 3, Hiberna 4, Pyribenzamin 3 and Venacalcium B_6 10. Samples of plasma and serum were separated from the blood of the identical animals supplying samples for the morphological examinations. The results are shown in table 3.

Surveying the data, one finds no striking characteristics in total protein and its fractions, in mineral substances and in glucose, while the histamine concentrations alone might be considered to decrease by degrees after the injections of antihistamine preparations. The average values of each treated group before treatment were 2.76~3.63 γ/ml. At just end of the injections the values indicated 2.13~2.84 γ/ml and at 7 and 14 days after the injections they were measured as 1.70~3.07 γ/ml and 1.15~2.72 γ/ml respectively. Gradual decrease of the blood histamine concentrations was noted in the treated animals which were sprayed sufficiently with insecticides, but in the samples taken from the relapsed cases at 1 or 2 weeks after the end of the injections, there were found re-increases in histamine concentrations.

TABLE 3. *Variations of Serum Composition in the Course of the Treatment*

DIVISION		NO. OF CASES	TIME OF EXAMINATION	SERUM ANALYSIS											PLASMA	
				T.P.*	Al.*	Gl.*	Gl.-fraction* α	Gl.-fraction* β	Gl.-fraction* γ	A/G	P**	Ca**	Na**	K**	Gluc.**	Hist.***
Non-treated Group	Healthy	10	Midsummer	6.92	2.28	4.64	0.97	1.68	1.98	0.49	3.2	11.9	317.0	17.8	71	1.14
	Patients	24		7.00	2.15	4.85	1.00	1.74	2.11	0.45	3.5	12.7	323.9	17.0	78	3.89
Treated Group	Allergin	3	Pre-injec.	7.20	2.18	5.04	1.03	1.92	2.09	0.43	3.2	12.9	302.5	16.2	84	3.03
			Just post-injec.	7.40	2.26	5.14	1.17	1.88	2.09	0.44	2.8	13.2	308.7	16.3	75	2.41
			7th day post-injec.	7.30	2.15	5.15	1.04	2.05	2.06	0.42	3.1	12.9	298.7	16.0	73	3.07
			14th day "	7.33	2.16	5.17	1.12	1.93	2.12	0.42	3.2	12.9	276.2	16.0	76	2.72
	Vena-calcium B_6	10	Pre-injec.	7.11	2.27	4.84	0.98	1.73	2.13	0.47	3.5	12.6	331.0	15.8	78	3.63
			Just post-injec.	7.04	2.19	4.85	1.04	1.74	2.07	0.45	3.7	12.6	323.0	18.2	75	2.84
			7th day post-injec.	7.01	2.26	4.81	1.04	1.76	2.01	0.47	3.6	12.6	315.2	16.8	72	2.79
			14th day "	6.93	2.24	4.69	1.03	1.76	1.90	0.48	3.5	12.8	313.7	16.2	75	2.67
	Hiberna	4	Pre-injec.	6.75	2.16	4.59	1.03	1.70	1.86	0.47	3.5	13.5	319.0	18.1	74	3.12
			Just post-injec.	6.95	2.15	4.80	1.08	1.74	1.98	0.45	3.3	12.8	323.0	18.7	75	2.29
			7th day post-injec.	6.85	2.11	4.74	0.98	1.72	2.04	0.45	3.1	12.8	315.2	17.7	70	2.46
			14th day "	6.95	2.19	4.76	0.98	1.77	2.01	0.46	3.3	13.5	313.7	17.9	69	2.61
	Pyri-benzamin	3	Pre-injec.	6.93	1.99	4.93	0.98	1.65	2.31	0.40	3.6	12.4	355.0	16.7	81	2.76
			Just post-injec.	7.27	2.05	5.27	1.03	1.76	2.43	0.39	3.3	12.2	342.0	15.8	75	2.13
			7th day post-injec.	7.13	2.02	5.11	1.04	1.73	2.34	0.40	3.5	12.7	325.0	17.4	78	1.70
			14th day "	7.50	2.10	5.40	1.01	1.74	2.65	0.41	2.8	13.4	325.0	16.7	77	1.15
	Average	20	Pre-injec.	7.04	2.21	4.83	1.00	1.75	2.08	0.46	3.5	12.9	327.2	16.5	79	3.31
			Just post-injec.	7.12	2.18	4.93	1.06	1.76	2.11	0.44	3.4	12.7	328.8	17.8	75	2.55
			7th day post-injec.	7.05	2.15	4.89	1.03	1.78	2.08	0.44	3.4	12.8	314.0	17.0	73	2.61
			14th day "	7.06	2.21	4.85	1.03	1.78	2.04	0.45	3.4	13.2	309.4	16.6	75	2.54

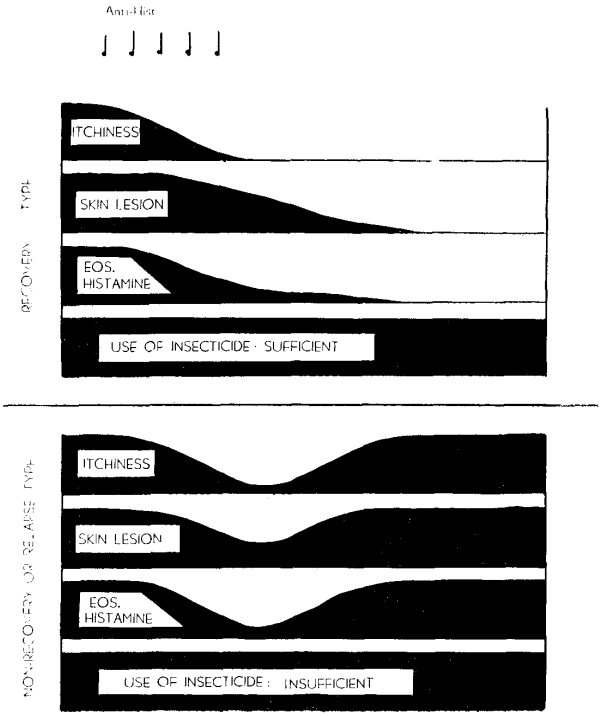
Note: *…g/100 ml. **…mg/100 ml. ***…γ/ml.

Discussion

As was reported in the previous paper[6], significant results have been gained in the preliminary therapeutical experiments concerning the applications of antihistamine preparations for the animals affected with "kasen". So in 1957, the authors have conducted practical studies on the applications to many affected patients in the fieled. To generalize, the decrease or disappearance of itchiness in the lesions occurred on the 3rd or on the 4th days from the commencement of the injections and the lesions tended to recovery by degrees. However, when sufficient spray of insecticides was not continued in parallel with the injections or when the spraying was given up, the itchiness reappeared within several days after the injections. Moreover, the variations in eosinophile numbers and in histamine contents ran parallel with variation of the itchiness; both blood constituents of the affected horses indicated higher values than in the normal horses.

Observing the above described data, these findings were identical with those of the results obtained from the preliminary experiments[6]. Riek[7,8] reported that the cause of the equine allergic dermatitis in Australia which is similar to "kasen" is a hypersensitivity to the bites of bloodsucking insects, *Culicoides robertsi*; he said the injections of antihistamine preparations and the spray of DDT were

Table 4. *Healing Mechanism of "Kasen"*



beneficial for treating the disease. In Hokkaido, though the real cause of "kasen" is not yet known, the authors are of the opinion that "kasen" is an allergic disease due to the facts obtained from their investigations to the present day.

It is considered, as ISHIHARA and UENO state, that the disease attacks only some horses having a predisposition. YAMASHITA and co-workers collected several species of sandfly infesting the lesions of the affected horses and they are now doing research on the etiological relations. Accordingly, as reported in the previous paper, it is accepted that there are close connections among the itchiness, the skin lesions, eosinophile counts, blood histamine contents and bloodsucking insects respectively. Therefore, the therapeutic methods employed by the writers in treating this disease may be thought to be reasonable. Especially, the use of antihistamine drugs and extermination of bloodsucking insects are most significant elements of the treatment. Summarizing the results of the experiments, the mechanism of healing of the disease may be shown as in table 4.

SUMMARY

The authors have conducted practical treatment of field horses affected with "kasen" in the summer of 1957. The results thus obtained may be summarized as follows.

1. Antihistamine preparations, for instance Allergin, Hiberna, Pyribenzamin and Venacalcium B_6 were used for the treatment of "kasen" in the amount of 200~300 mg per day for 5 days as real volume of the substances; the cases were observed 16~25 days after the injections.

2. Thirty-six cases out of 44 affected horses recovered completely and 6 cases relapsed despite the treatments. However, the conditions of 2 cases were unchanged in comparison with pre-treatment conditions.

3. In the recovered cases, insecticides, for instance DDT and BHC powders, were sprayed over the skin surface sufficiently, especially in the long hair areas and in the vicinity of the stables throughout the period of experiments. However in the relapsed and unchanged cases the use of insecticides was insufficient or quite neglected.

4. The values of eosinophile counts and histamine concentrations were higher in affected horses than in non-affected horses. After the patients were injected with antihistamine drugs the two constituents ran almost parallel with the variations of the clinical signs. Eosinophile numbers and histamine concentrations were increased in the relapsed cases within several days after the end of the injections.

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FIG. 1. *State of Pre-treatment in the Neck*

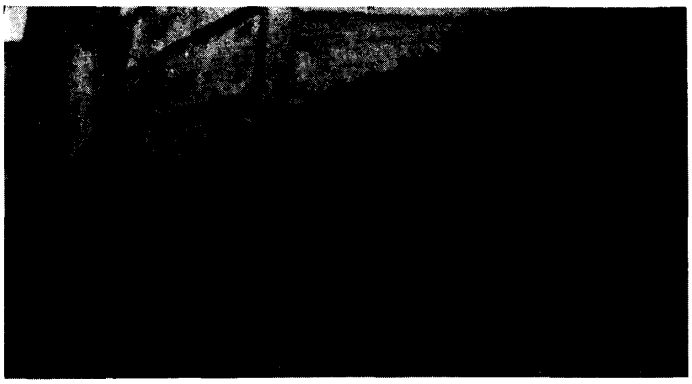

FIG. 2. *State at 14 Days in Post-treatment in the Neck.*

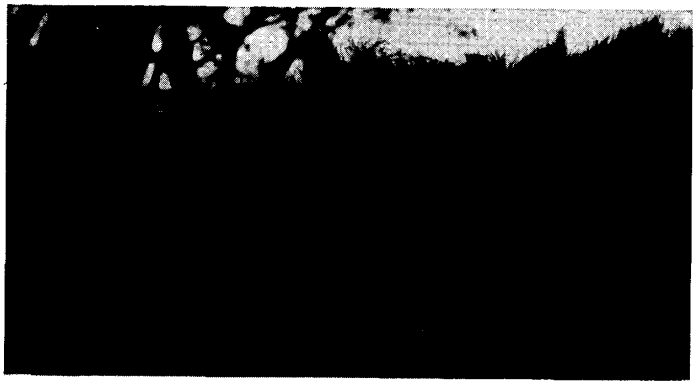

FIG. 3. *State of Pre-treatment in the Tail*

FIG. 4. *State at 14 Days in Post-treatment in the Tail*