STUDY ON THE SLOW RHYTHM FOUND IN THE PULSE AND RESPIRATION INTERVALS OF RABBITS

II. ON THE CHANGES OF THE SLOW RHYTHM INDUCED BY SOME EXPERIMENTAL TREATMENTS

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As an approach to the understanding of the mechanisms regulating movement in the living body, the theory and the method of automatic control have been applied. Particularly, this has been done in the field of electromyographic study; mass of valuable information has emerged. Thus, the slow undulation[13] found in abnormal EMG is now known as a disturbance of the central nervous servomechanism.

This mode of procedure has also been applied to other phenomena, such as the series of pulse and respiration intervals as described in the present writer's preliminary report[10], but reports concerned with respiration intervals have appeared in relatively few cases. Furthermore, simultaneous determination of pulse and respiration intervals has been reported only by TOHI (1951) who suggested a certain interrelationship between the fluctuation of pulse and respiration intervals from his one case measurement in which he used a man.

In the present writer's preliminary report[10], the author described an experiment which was aimed mainly to examine the method of analysis and the characteristics of the slow rhythm found in rabbits in the untreated prone position. In the present paper, there are described in detail the findings drawn from the analysis of periodicities included in pulse and respiration intervals time series using simultaneous records made of these intervals in supine position, drugs administered and surgically treated rabbits.

Then, these results, mainly the occurrences and frequency distributions of the periods of these slow rhythms, and the correlation between the slow rhythms of pulse and respiration intervals were examined and compared with the results set forth in the preliminary report; the occurrence mechanism of the slow rhythms is discussed.

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MATERIALS AND METHODS

The experimental animals, the method of recording, the procedure in analyzing the time series, the judgement of periodicity and the method of classification of periodicity are the same as those described in the preliminary report[10].

First of all, the animals were fixed in the positions, either untreated prone (a) or supine (b), and the control records were made.

(a) Untreated prone position—ECG and pneumograms were recorded at 45 min. after the untreated rabbits had been fixed in a prone position in cylindrical metal fixing apparatus. The animals were fixed in this position, only at their cranial part in order to allow their position to be as nearly natural as possible.

(b) Untreated supine position—Animals were placed in a supine position in which their legs were bound and fixed by means of a wooden rabbit-fixing apparatus, and the records were made at 45 min. after fixation. The untreated prone position was used as the control position of this experiment and in addition, this position was also used as a control of some other experimental treatments.

The following recordings were taken immediately after these control recordings in the same positions as those of the controls under respective described experimental conditions.

(c) At 15 min. after chlorpromazine (20 % Wintamin 10 mg/kg body weight) intramuscular injection, records were made with animal in prone position.

(d) At 5 min. after trans-π-oxocamphor (0.5% Vitacamphor 1 mg/kg body weight) intravenous injection, records were made with animal in prone position.

(e) At 10 min. after thiopental sodium (2.5% Ravonal 30 mg/kg body weight) subcutaneous injection, records were made with animal in supine position.

(f) At 30 min. after urethane (10% urethane aqueous solution 1 g/kg body weight) subcutaneous injection, records were made with animal in supine position.

(g) At 5 min. after strychnine nitrate (0.1% strychnine nitrate 0.12 mg/kg body weight) intravenous injection, records were made with animal in prone position.

These administrations were performed according to the directions (1) of TOMINAGA (1956) for chlorpromazine, trans-π-oxocamphor and thiopental sodium, (2) of KATO (1947) for urethane since he could induce periodic fluctuations of respiratory level by injection of the same dose, and (3) of ARDUINI and ARDUINI (1954) for strychnine nitrate.

(h) Experimental acute anemia was brought about as follows. About one-fourth of the estimated total blood volume of the rabbit, which was calculated on the basis of the data of BURKE (1957), was bled. At one hour after the operation, records were made with animal in the supine position.

(i) Precollicular decerebrations were performed under light anesthesia by means of ether inhalation. Forty-five minutes after the operation, recordings in prone positions were taken, and 45 min. after that, recordings in supine position were taken.

EXPERIMENTAL RESULTS

1 The Average Intervals

The following examinations were made using pulse and respiration average intervals of each measured 120 intervals, that is to say, the mean values of 120 respiration intervals were used as the average respiration intervals, and the mean values of 120 pulse intervals were used as the average pulse intervals.

Correlation between the two average intervals and the standard deviations of each series is shown in fig. 1. In this figure, no correlation between them was recognized as to the average respiration intervals.

As to the average pulse intervals of the untreated prone position, a correlation could be seen which was similar to that of $\bar{\tau}$-S curve found in discharge intervals of NMU; viz., the standard deviations were nearly constant when the average pulse intervals were shorter than about 0.26 sec., and when the intervals were longer than 0.26 sec., there was a definite tendency, that the longer the intervals, the larger the standard deviations. Such correlation did not appear as to the average pulse intervals of the untreated supine position and urethane injected animals; in the cases of some drugs administered animals in the prone position, no part in the curve where the standard deviations were nearly constant was observed, that is to say, the curve tended to a sloping straight line.

In these experiments, however, one exception appeared as shown in the right upper curve of fig. 1 as a and b. This occurred in the case of the same individual rabbit.

No correlation between average intervals and body weight, room temperature, and between each average interval was observed.

2 The Decerebration Experiment

The correlograms obtained from the records of precollicular decerebrated rabbits are shown in fig. 2. From the results shown in the figure and table 1, it can be concluded that the slow rhythms could occur without the existence of central nervous system higher than the nasal end of *Colliculus rostralis*, in the supine and prone positions.

3 The Number of Components Included in a Series

Slow rhythms were classified into 4 groups, A, B, C and D, using the same mode of classification as that of the preliminary report[10], by taking into consideration the forms of the correlograms. The average number of components included in a series pertaining to groups A, B and C respectively and the percentage occurrences of slow rhythms pertaining to group D were shown in table 1. The percentage of occurrences of the frequency components which are composed with periods of 2 terms (2 term component) is shown in this table in parenthesis.

a) The 2 term component

As shown in the table, few cases of 2 term components which had high regularity (groups A and B) were observed in respiration slow rhythm. Thus, the 2 term component frequently occurred with low regularity.

The frequency of occurrence in group C was high in the supine position, trans-π-oxocamphor, strychnine nitrate injected and acute anemia, and low in chlorpromazine injected animals.

FIG. 1 *Correlation between Average Intervals and Standard Deviations*

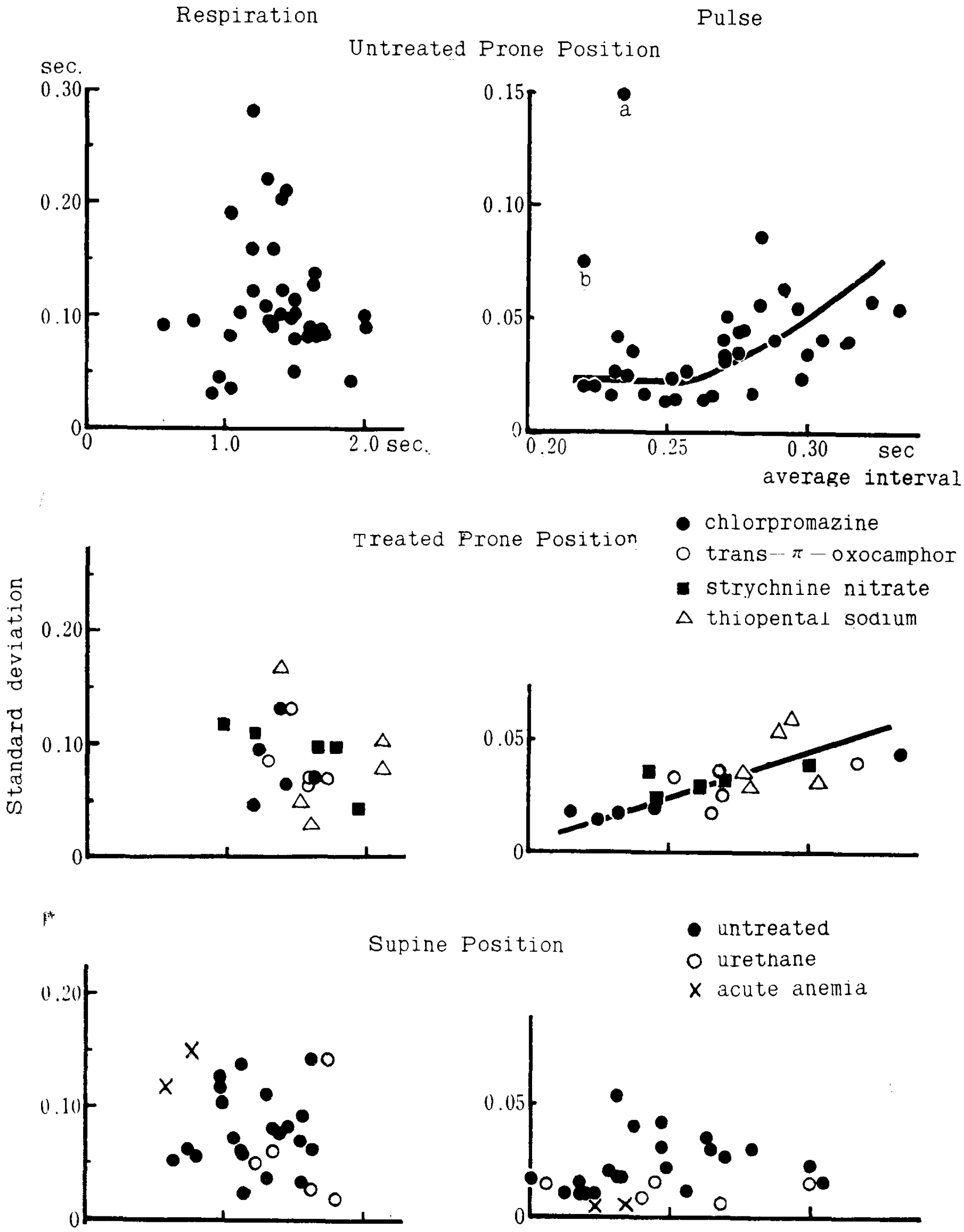


FIG. 2 *Slow Rhythms Found in Decerebrated Rabbit (prone position)*

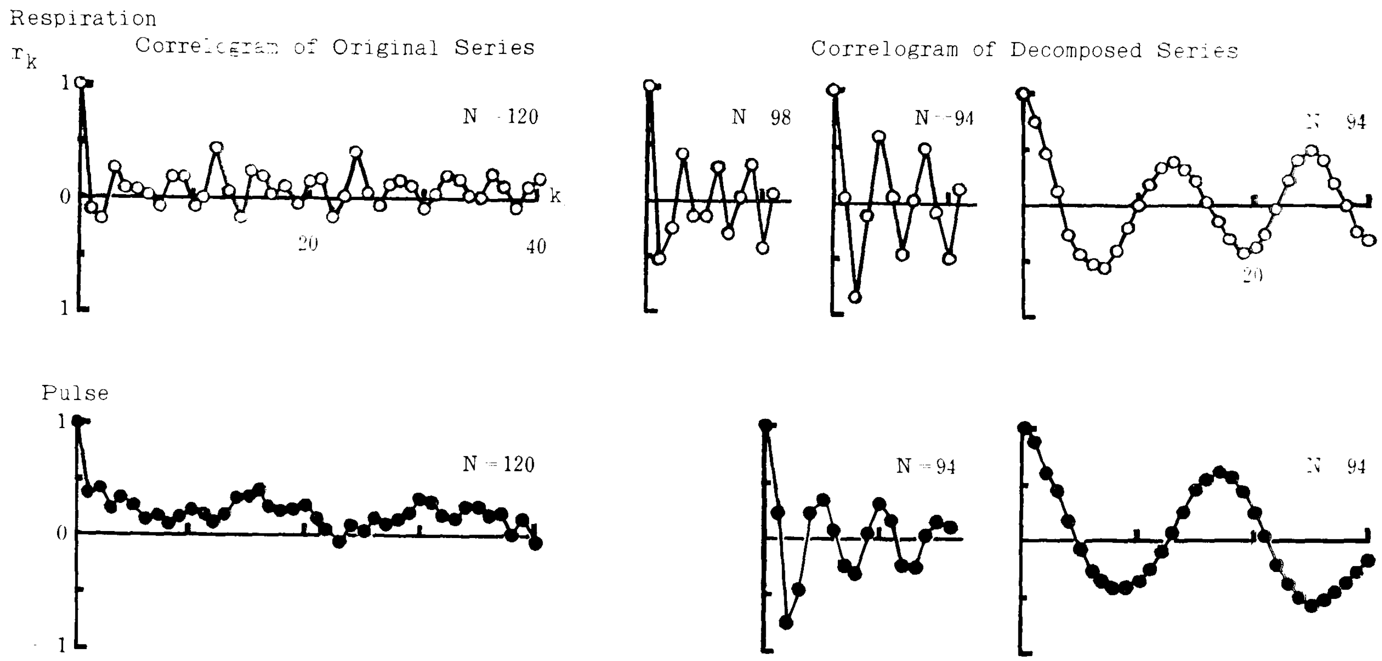


TABLE 1 *Occurrence of Slow Rhythms*

GROUP	N	RESPIRATION A (%)	RESPIRATION B (%)	RESPIRATION C (%)	RESPIRATION D %	PULSE A	PULSE B	PULSE C	PULSE D %
Untreated Supine Position	21	0.6 (0)	1.0 (0)	2.1 (80)	52	0.3	1.0	1.9	38
Chlorpromazine	5	0.4 (20)	1.0 (20)	2.2 (20)	0	0.6	1.2	1.8	80
Trans-π-Oxocamphor	5	0.4 (0)	1.2 (0)	1.8 (80)	40	0.6	1.8	2.4	100
Thiopental Sodium	5	0.4 (0)	1.8 (0)	2.6 (40)	20	0.4	1.4	2.6	40
Strychnine Nitrate	5	0.0 (0)	0.8 (20)	1.8 (80)	80	0.0	0.8	2.2	40
Urethane	5	0.4 (0)	0.8 (0)	2.0 (60)	40	0.0	0.4	0.6	0
Acute Anemia	2	0.0 (0)	0.0 (50)	0.5 (100)	0	0.0	0.5	0.5	0
Decerebration Prone Position	3	1.7 (0)	1.7 (0)	2.3 (33)	100	1.0	1.3	2.3	67
Supine Position	1	1.0 (0)	1.0 (0)	1.0 (100)	100	1.0	1.0	2.0	0

b) The component having periods above 3 terms

In respiration, as shown in table 1, the marked phenomenon throughout groups A, B and C was that less components appeared in acute anemia than in the other cases. As for group D, the percentage of occurrences was the most in strychnine administered, intermediate in the supine position, trans-π-oxocamphor and urethane, and non-existent in the cases of chlorpromazine and acute anemia administration.

In pulse intervals, as for groups A, B and C, the number of components included in a series were approximately the same as in the case of respiration, but there is one exception that the number of components detected in urethane were less than in respiration, as well as in the case of acute anemia. Nevertheless, in group D, somewhat different results were obtained between respiration and pulse, viz., many components were detected in trans-π-oxocamphor (100%) and chlorpromazine administration, and none in urethane and acute anemia.

Figures 3, 4 and 5 show the changes in number of components included in a series induced by the positional change, drugs administered and operative treatment.

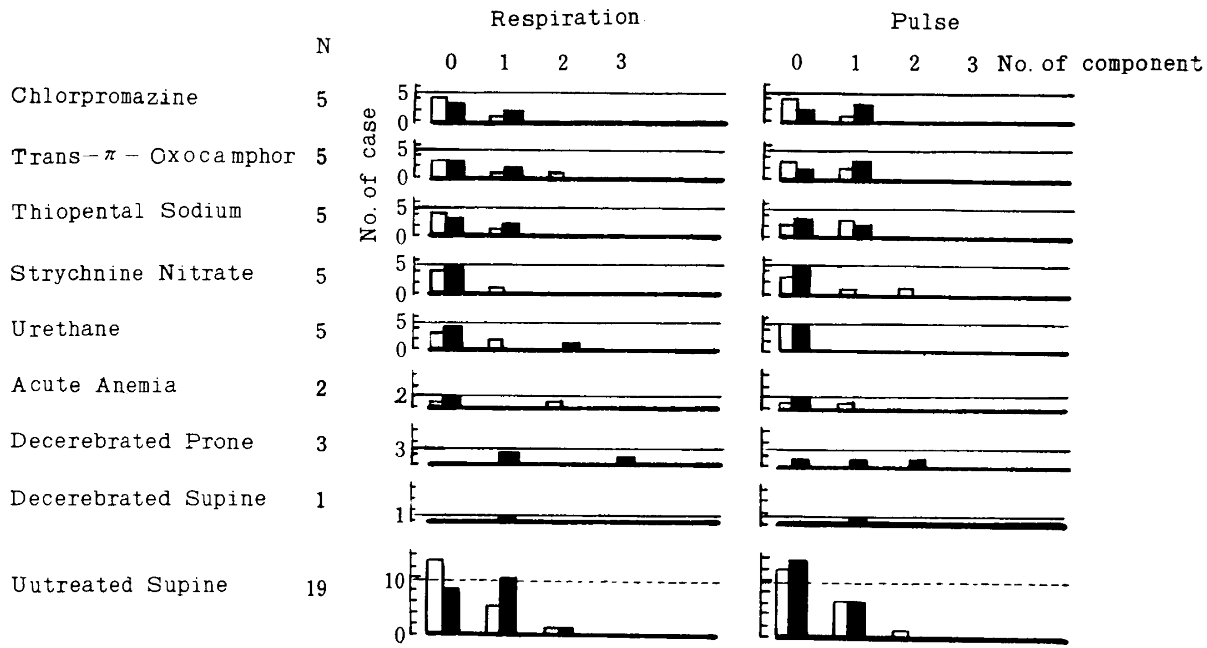
Group A: In respiration, when the position of the animals was changed from prone to supine, slow rhythm tended to occur. In pulse, there was a tendency for the slow rhythm to be brought about by chlorpromazine and to be caused to disappear by strychnine nitrate administration.

Group B: As a result of the positional change, the number of frequency components included in a time series of respiration intervals tended to decrease slightly, and to increase in pulse.

From this and the results obtained with group A, it might be concluded that a relatively high occurrence of the components which had full regularity was obtained in respiration as a result of the positional change of the rabbits.

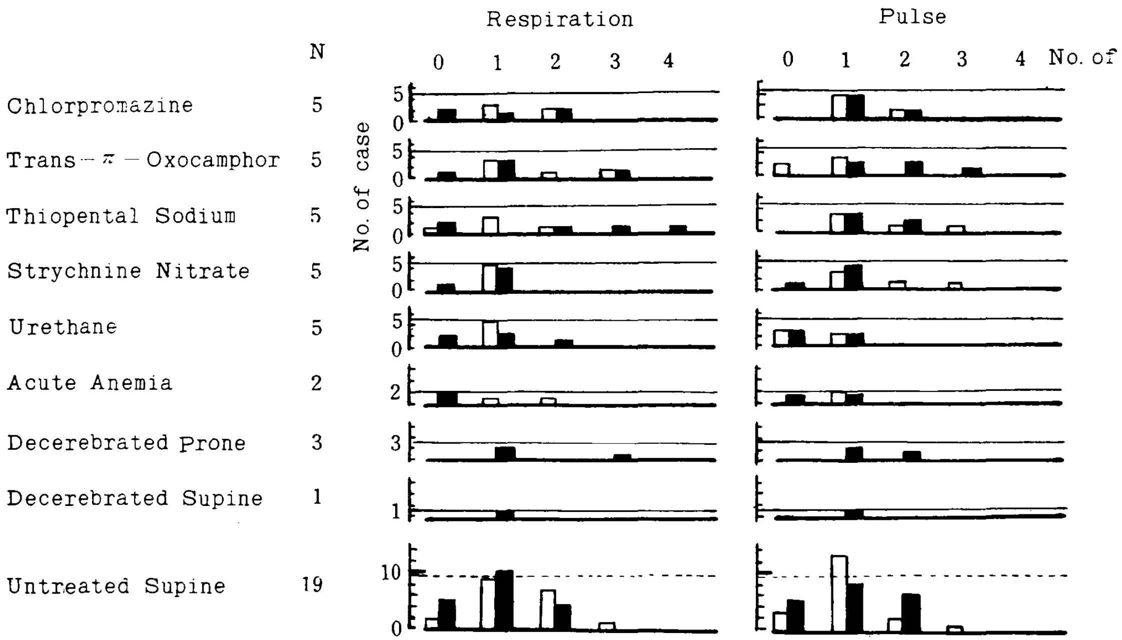
In the other experiments, it was noted that slow rhythms tended to be caused to disappear by the treatment of acute anemia in respiration and to increase by the injection of trans-π-

FIG. 3 *Change in Number of Components Included in a Series (group A)*



Notes: N: Total number of the cases examined
Empty column: Control
Black column: Treated

FIG. 4 *Change in Number of Components Included in a Series (group B)*



Notes: N : Total number of the cases examined
Empty column : Control
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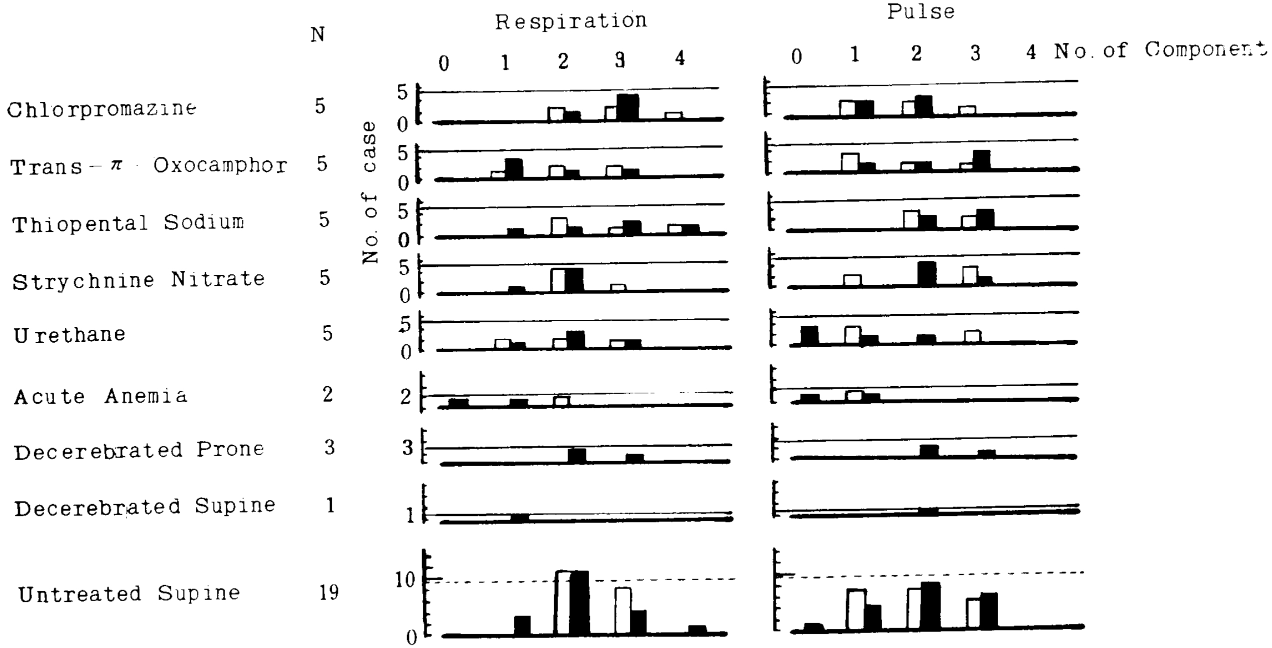
FIG. 5 *Change in Number of Components Included in a Series (group C)*



Notes: N : Total number of the cases examined
Empty column : Control
Black column : Treated

oxcamphor in pulse.

Group C: The number of components in respiration tended to decrease as a result of the injection of trans-π-oxocamphor, and because of acute anemia, and resultant from the injection of urethane in pulse, the number tended to increase at the time of the injection of trans-π-oxocamphor.

Group D: Table 2 shows the numbers of respective cases in which periodicity, detected from the correlogram of original series affected by some treatments, appeared ($- \rightarrow +$), disappeared ($+ \rightarrow -$) and did not change. In respiration, there was noticed a certain tendency which disappeared in chlorpromazine administration and similarly in thiopental sodium, and remained unchanged in cases of acute anemia.

TABLE 2 *Change of Slow Rhythms Detected from Original Series*

	RESPIRATION				PULSE				N
CONTROL	+	+	−	−	+	+	−	−	
TREATED	−	+	+	−	−	+	+	−	
Untreated Supine Position	3	4	5	7	7	5	3	4	19
Chlorpromazine	3			2	1	4			5
Trans-π-Oxocamphor	2	1	1	1		3	2		5
Thiopental Sodium	1	1		3	1	2		2	5
Strychnine Nitrate		3	1	1	3	2			5
Urethane	1	1	1	2				5	5
Acute Anemia				2	2				2
Total	10	10	8	18	14	16	5	11	46

In the pulse, there was a tendency that occurred in trans-π-oxocamphor administration, disappeared in strychnine nitrate and in acute anemia and remained unchanged in urethane. In general, there was a tendency in the pulse for the slow rhythms to disappear more readily than to occur under these treatments.

No correlation between the number of components and average intervals, standard deviations of intervals, body weights and room temperatures was recognized.

4 The Periods of Slow Rhythms

In this report, the periods of slow rhythms were classified into 2 groups: one had a comparatively longer period component of over 15 sec., 10 terms in respiration and 15 sec., 50 terms in pulse, and the other had a shorter period component which had a shorter period than that of the longer period component.

Supine position: In respiration, groups A and D showed a marked increase of shorter period component and the distribution figure (fig. 6) showed a uniform and wide distribution when the periods were shown with use of time. And when the periods were shown with use of term number, two peaks in the distribution figure became apparent in group A. Groups B and C showed a marked disappearance of longer period components, when they were shown by use of time and term.

In the pulse, generally, the tendencies of which were similar to those of respiration intervals were observed, but different features were obtained in the following two points. Group A lacked the peak of longer period which appeared in the case of respiration, and a small number of longer periods (about 30 sec. or 90 terms) appeared in groups B and C.

Thus, in general, these results showed a tendency that, when the position of the rabbits was changed from prone to supine, the longer period components of the slow rhythms of respiration and pulse intervals disappeared and the shorter period components appeared.

When the animals were given some drugs and operative treatment, the following marked changes of the periods were noted (figs. 7, 8, 9 and 10).

Chlorpromazine: In both respiration and pulse, a tendency for the longer period components to disappear and the shorter period components to appear was observed in groups A, B and C.

Trans-π-oxocamphor: Different features were obtained between respiration and pulse.

That is to say, in pulse intervals, the distribution pattern was divided into longer and shorter period components in all 4 groups. In contrast with that, in respiration intervals, the numbers of both longer and shorter period components diminished and the components which had intermediate period between them increased.

Urethane: In respiration, there was observed a tendency for the periods to shorten in group C only when the periods were shown with use of term. In the pulse, marked disappearance of the shorter period components was observed in group C.

Using the periods of group D, for the reasons set forth in the preliminary report, the writer examined the correlations between the periods and other determined data and reached conclusions as follows.

a) No correlation was observed between body weights, room temperatures, average intervals and standard deviations and the periods pertaining to group D.

b) The correlation between the pulse numbers corresponding with on respiratory cycle and the periods is shown in fig. 11. Significant correlations (ratio of risk was 10%) were obtained in both pulse and respiration, except in the case of respiration as denoted by use of terms.

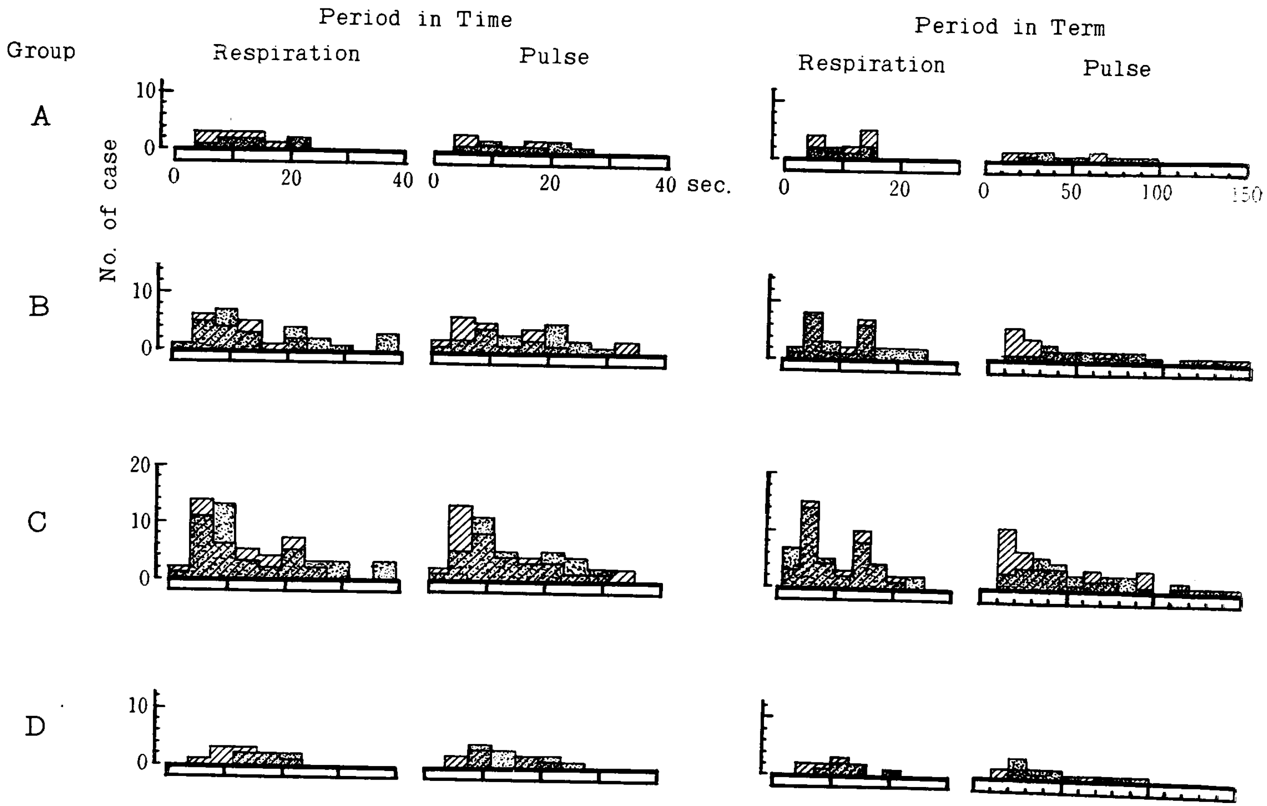
c) The correlation between the periods of pulse and respiration slow rhythms which was detected simultaneously from both of the original series is shown in fig. 12. The significant proportional correlation between the two periods was recognized (the ratios of risk were 5% and 1% when the periods were denoted by use of time and term, respectively). When the periods were denoted by use of time, the mean value of the two periods was nearly equal, and half of these cases appeared with almost the same period.

Discussion

Consideration being given to results reported in the preliminary report[10], the following discussion is presented.

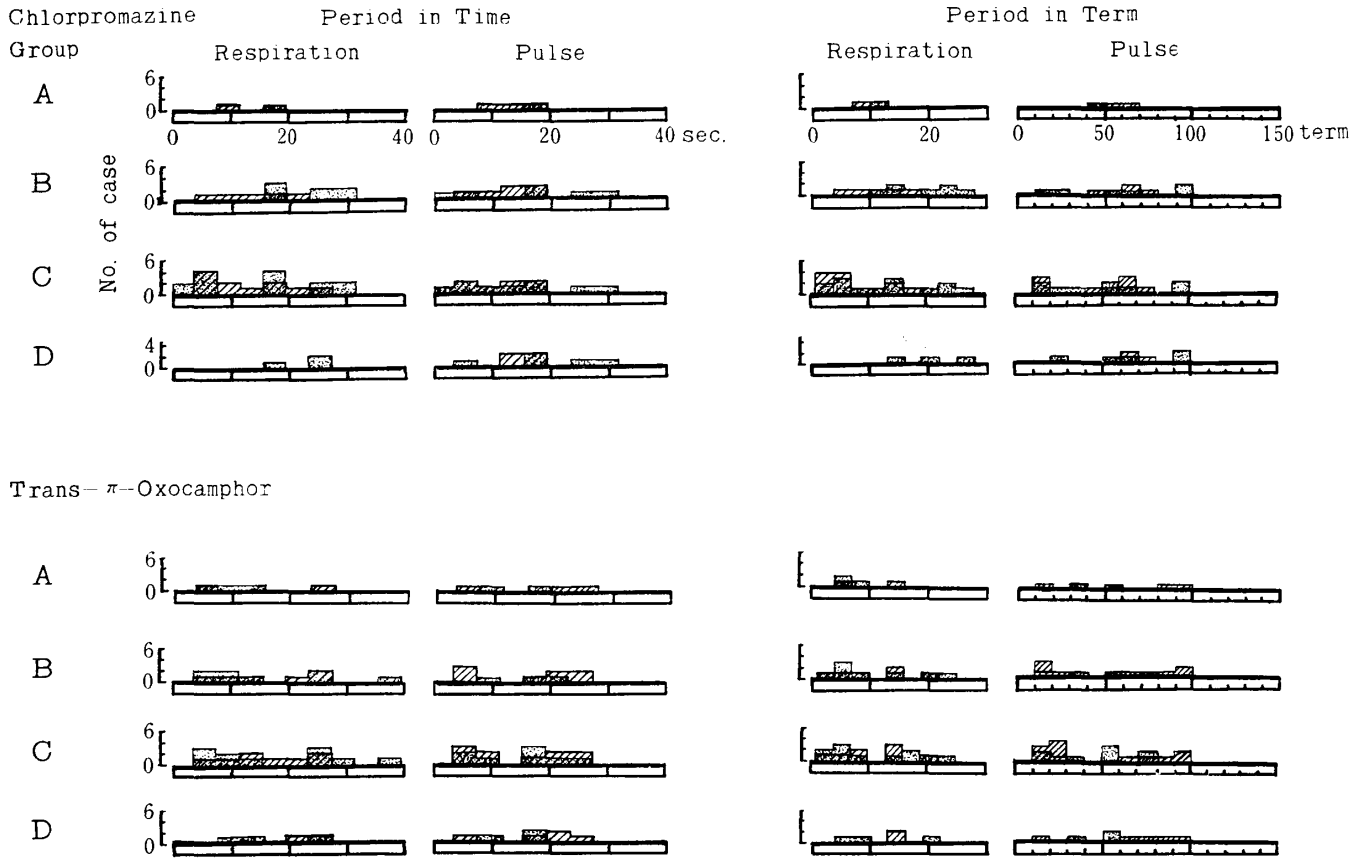
On the 2 term component: This fluctuation is a series that is linked alternately with longer and shorter intervals, and it is thought that it reflects the functional activity of an automatic regulation mechanism acting to minimize the fluctuation

FIG. 6 *Change in Period Induced by Positional Change*



Notes: Dotted column: Control
Hatched column : Treated

FIG. 7 *Change in Period Induced by Administration of Drugs*



Notes: Dotted column : Control
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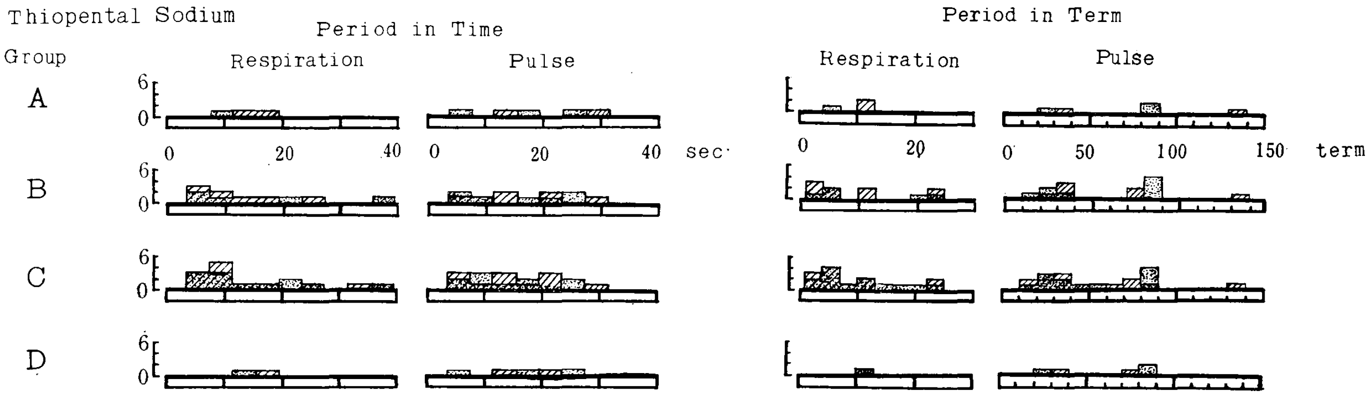
FIG. 8 *Change in Period Induced by Administration of Drugs*



Notes: Dotted column : Control
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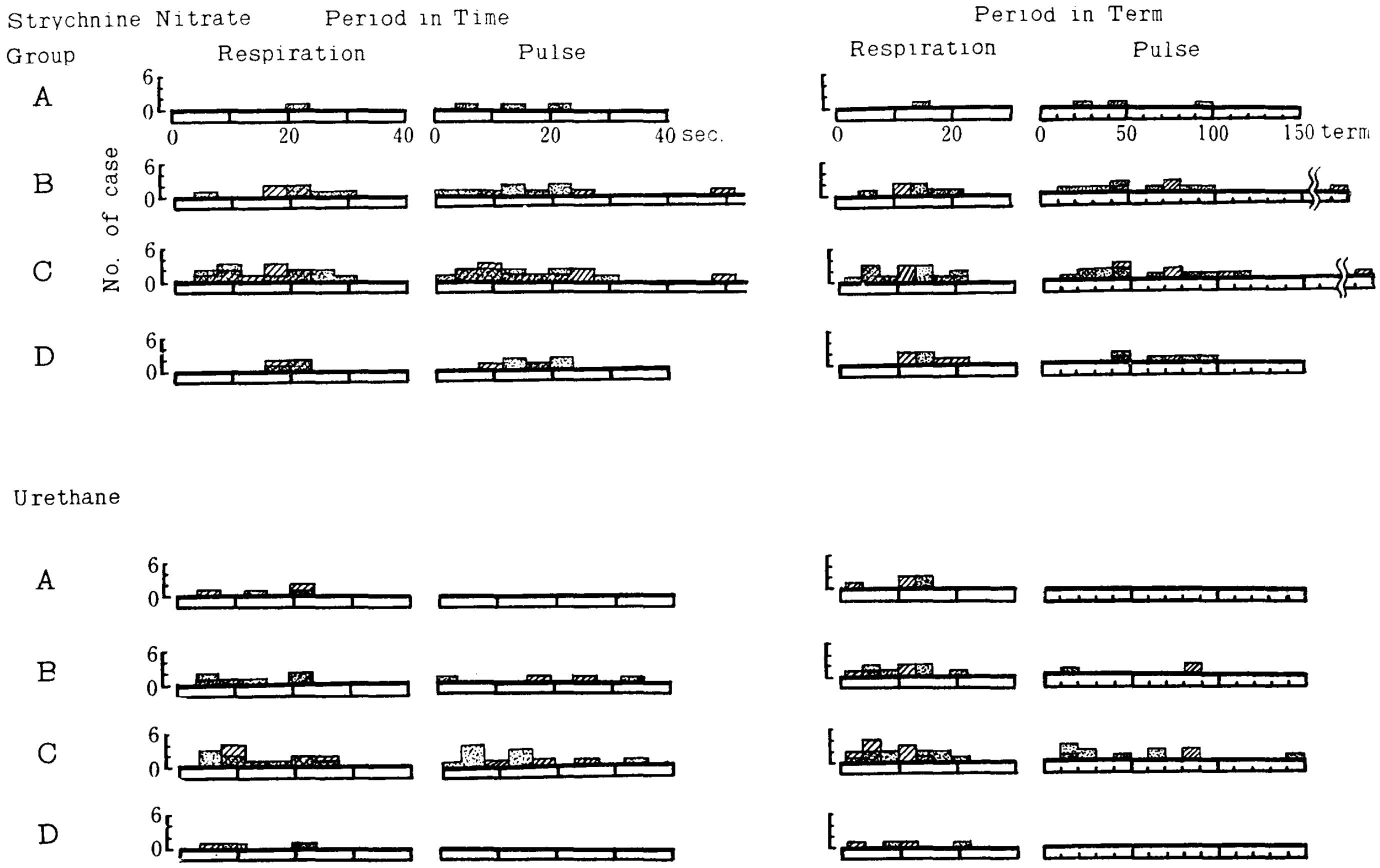
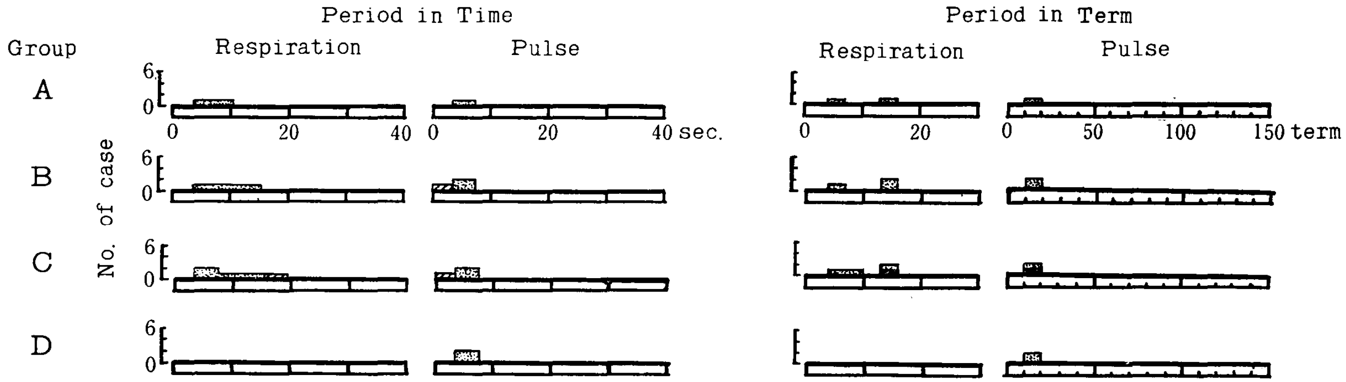
FIG. 9 *Change in Period Induced by Administration of Drugs*



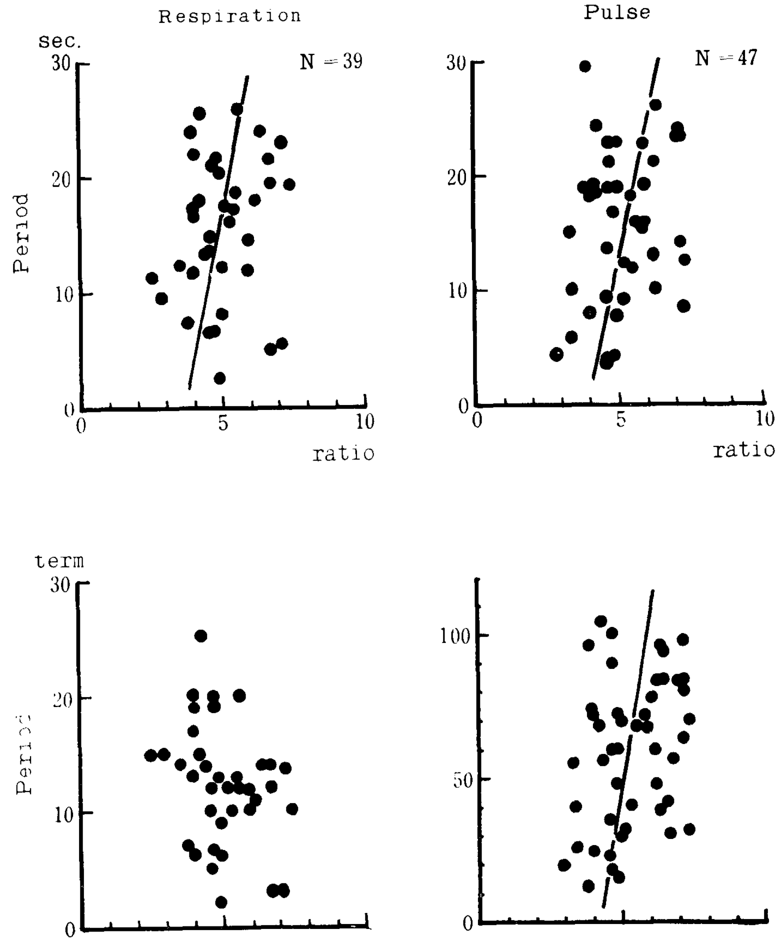
Notes: Dotted column : Control
Hatched column : Treated

FIG. 10 *Change in Period Induced by Experimental Acute Anemia*



Notes: Dotted column : Control
Hatched column : Treated

FIG. 11 *Correlation between Ratios of Respiration Interval to Pulse Interval and Periods of Slow Rhythm (group D)*

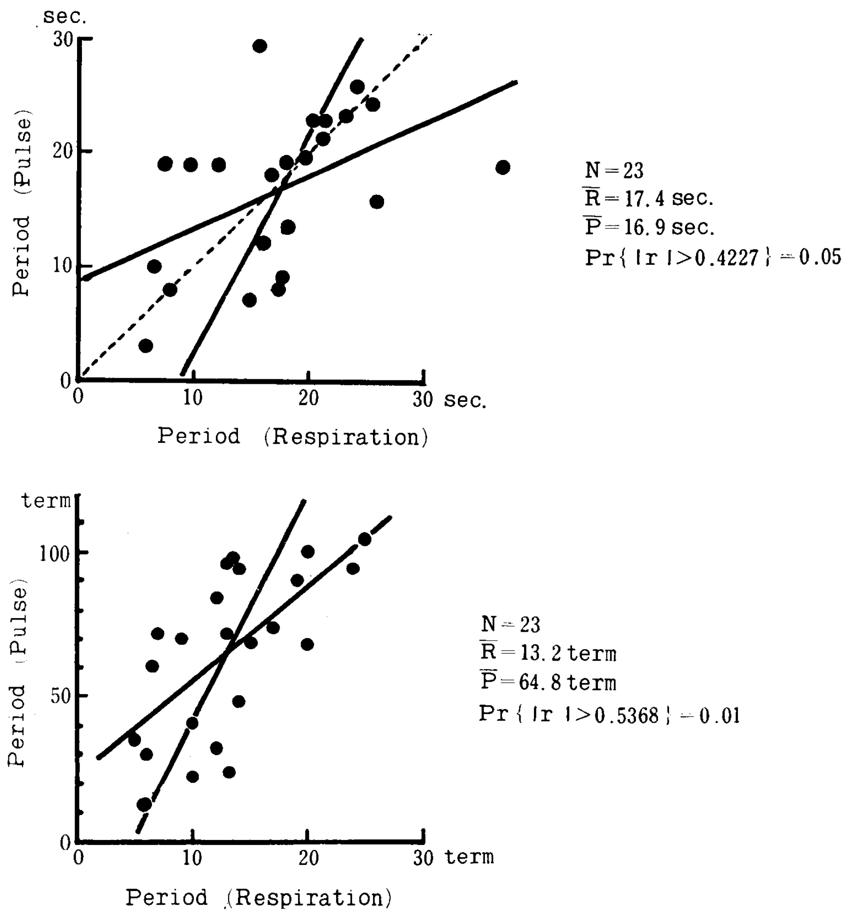


of respiration intervals.

In the present results, 2 term components occurred with comparatively high frequency in the condition of supine position, trans-π-oxocamphor, strychnine nitrate injections and acute anemia, and low frequency in chlorpromazine injections.

It has been reported that strychnine had an inhibitory effect upon IPSP induction of spinal synapses[3] and had an enhancing effect upon the response of brain stem medial reticular formation to peripheral stimulation[1]. Since the supine position is unnatural, it can easily be expected that increased afferent impulses from peripheral portion will be generated and reach to the reticular activation system as proposed by MAGOUN; thus the nerve centers included in this system may enforce their excitability. On the other hand, the pharmacological action of chlorpromazine is thought to act upon the brain stem reticular activation system which is situated between the *medulla oblongata* and *hypothalamus* and to inhibit the action of the

FIG. 12 *Correlation of Periods (group D)*



system[11,12].

In consideration of these findings and the present results, it may be estimated that 2 term component tends to occur more or less in the condition of reticular excitation, and vice versa in the depression. Thus, it might be suggested that the components of respiration slow rhythms have a close relationship to the excitability of the brain stem reticular activation system. And then, the fact that the components occurred with high frequency as a result of injection of trans-π-oxocamphor might support the idea that this drug may enhance the excitability of the respiration center located within the brain stem reticular formation as some reports have suggested[4].

On the components having periods above 3 terms: As described previously, there exist two divided groups in the frequency distribution figures of groups B and C, viz., shorter period and longer period component. The former component tended to occur markedly in both pulse and respiration intervals when the position of the animals was changed from prone to supine. The components had relatively high regularity in their periodicity, and at the same time, the latter components tended to disappear inversely as a result of this positional change.

The shorter period component had almost the same range of period as the periodic fluctuations described by KUSACHI (1954) in R-R intervals of ECG, by TOMINAGA (1956) in R-R intervals of cardiotonic ECG, by OKABE and TOMINAGA (1955) in R wave height in ECG and by OKABE et al. (1955) in phonocardiogram, in supine position.

Thus the marked shorter period slow rhythm might be estimated to occur with contribution of ascending impulses induced by binding the legs of the animals, by pressing the back of the animals, by disturbance of blood stream and so on because of the positional change in which a certain modulation of pulse and respiration regulation mechanisms occur.

The latter, longer period component occurred comparatively fewer times than the shorter period component both in pulse and respiration intervals, especially in the supine position.

TOMINAGA (1956) reported that the fluctuation of pulse intervals (slow undulation) was caused to disappear by thiopental sodium administration, and suggested that the fluctuation of pulse intervals occurred because of a contribution of nervous activity of cerebral cortex and that it was concerned with the excitability of the nervous mechanisms which might be situated more centrally than the cardiac center, considering the pharmacological action of thiobarbital anesthetics. On the other hand, the present experiment showed the opposite result in this respect; the longer period component slow rhythms were recognized as a result of the same application procedure of the drug except but not of the position of the animals. Then, it is clear that the fluctuation can occur without the existence of any portion of the upper part of the brain higher than the upper end of the *Corpora quadrigemina*, namely, without the part above the limbic lobe and other cerebral basal nuclei.

From these considerations and the observation that the respiratory longer period components tended to disappear in groups B, C and D as a result of chlorpromazine administration, it might be estimated that the longer period component may probably occur as a result of contribution of the mechanisms of the reticular activation system which is situated between the *medulla oblongata* and *pons*.

In the present experiment, a significant correlation between periods of pulse and respiration slow rhythms was obtained and the periods of pulse and respiration slow rhythms were approximately the same in half of the cases in which pulse and respiration slow rhythms occurred simultaneously. TOHI (1951) described a different result that the relationship of the periods between respiration and pulse fluctuation was 2 to 1, from his one case measurement in which he used a man. Apart from the disagreement, estimating the close locality of concerned autonomic centers such as the cardiovascular center and the respiratory center, it can be expected that a close mutual relationship between the regulation mechanisms of respiration and pulse rate exists.

On the other hand, HOFF et al. (1952) suggested that the reticular substance may contribute to the action of central regulation not only for regulation of pulse rate but also for the other autonomic nervous system function including respiration and for the somatic motor system. MAGOUN (1954) obtained an equivalent potential in the same portion of reticular formation by some different kinds of afferent stimulation. These approaches can be thought to provide enough evidence for the function of the reticular formation as a common denominator, and also, to support the present author's estimation which attached importance to the reticular formation for the occurrence mechanism of slow rhythms.

KATO (1956)[6] proposed the interference wave of pulse intervals induced by respiration for an occurrence mechanism of pulse interval fluctuation in rabbits. However, a large difference between pulse and respiration rates was noted in all of the present experiments, and even if the interference wave did exist, it must have had a very short period which could not be detected by the presently used procedure.

Nevertheless, it can be expected that the interference of the two intervals induced by a more complicated mechanism, which is other than the interference wave proposed by KATO, may exist and may play a certain role to the genesis of slow rhythm, since correlation was observed in this study between pulse numbers corresponding to one respiration and the periods of slow rhythm.

In comparison with the regulating ability of respiration and pulse intervals, it can be suggested that the latter is regulated more efficiently than the former from the correlation figure between average intervals and standard deviation of original series.

And then, from fig. 1, it may be thought that there exists a similar relation to that of $\bar{\tau}$-S curve[19] found in discharge intervals of EMG. That is to say, when the average pulse intervals are below 0.26 sec., this figure of untreated prone position shows less fluctuation and is distributed horizontally in the graph. Thus, the pulse intervals are being regulated efficiently when the pulses are rapid, as are also the discharge intervals of EMG. On the other hand, when the intervals are longer than 0.26 sec., there is a tendency that the longer the intervals become, the larger the standard deviation, and the regulating function is not operating any longer.

However, in the rabbits that were administered drugs (prone position), the horizontal part of the curve found in the untreated prone position rabbits was not seen, and inefficient regulation was shown. Thus, it can be estimated that the auto-regulating function was weakened in the rabbits administered some drugs of central action, either excitants or depressants, in the prone position.

Thus, the present author would suggest that the slow rhythms found in the present study represent a fluctuation which reflects the regulating function, particularly the functional situation of the living body. This further suggests inversely that there is an apparent possibility of examining the functional situation of the living body by detecting the slow rhythms.

However, it is said that pulse and respiration intervals of rabbits are so easily, suddenly and deeply affected by acoustic stimulation[5], lifting it in the arms[17] and other external stress or changes of environment, that it is necessary to monitor the experimental conditions strictly.

And then, since there remains some complication caused by the occurrence mechanism other than those described above, such as humoral factors and intrinsic factors induced by respective organs, especially the factors of cardiac pacemaker for pulse intervals, the periodic fluctuation induced by these factors should be considered and examined.

SUMMARY

Slow rhythms of pulse and respiration intervals of rabbits that are administered drugs and treated by experimental operations were detected; examination was made of the characteristics and occurrences of slow rhythms.

1. Correlation figure of average pulse intervals and standard deviation of the intervals showed a tendency that better regulation was performed within shorter intervals and worse in longer intervals in untreated prone position rabbits.

2. Two term components which seemed to reflect the regulation function of each respiration interval, occurred with high frequency under conditions of supine position, trans-π-oxocamphor, and strychnine nitrate administration and acute experimental anemia. The frequency was low in chlorpromazine administration.

3. Pulse and respiration slow rhythms could occur without the nerve centers higher than the upper colliculi of *Corpora quadrigemina*.

4. In the untreated supine position, slow rhythms of pulse and respiration intervals showed a tendency for the longer period component to disappear or for the shorter period component to occur, and shorter period and relatively regular slow rhythms became marked.

5. In chlorpromazine administration, there was a tendency for the relatively regular slow rhythms to become apparent and for the longer period component to decrease in both pulse and respiration slow rhythms.

6. In trans-π-oxocamphor administered animals, there was a tendency for the number of components included in a series of pulse intervals to increase; the

distribution figure of the period was divided into two groups separating at the point of about 15 sec., and 50 terms.

7. In urethane administered animals, there was a tendency for the shorter period component of pulse intervals to show a marked decrease. No slow rhythm could be detected on the correlogram of original series of pulse and respiration intervals.

8. Significant correlations between pulse number corresponding to a single respiration and period of slow rhythm was recognized in both pulse and respiration.

9. When pulse and respiration slow rhythms are detected simultaneously, the significant correlation between the two corresponding slow rhythms was recognized. About half of the two periods was nearly equal. From this fact, it can be supposed that there exists a close connection between the regulation mechanism of respiration and pulse intervals.

10. Some considerations on the occurrence mechanism of slow rhythms found in pulse and respiration intervals were discussed; it can be expected that the reticular formation situated between *medulla oblongata* and *pons* contributes to the genesis of slow rhythms.

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