MUSCLE EXERCISE AND THE HYPOTHALAMO-SYMPATHICO-ADRENOMEDULLARY SYSTEM*

WITH SPECIAL REFERENCE TO THE HOMEOSTASIS OF BLOOD SUGAR LEVEL FOLLOWING MUSCLE EXERCISE AND THE INTERRELATIONSHIP BETWEEN MUSCLE EXERCISE AND ADRENALINE

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The nervous and endocrine systems are interrelated, interact and cooperate structurally and functionally. When living subjects are exposed to changes in external and internal environments, these systems are activated immediately in a harmonious interrelationship in order to sustain the homeostasis of the vital being.

The autonomic nervous system has an intimate connexion with the endocrine glands in various ways and to various degrees, and also the internal secretion is under the regulatory mechanism of the central nervous system, especially of the hypothalamus. For this reason some anatomico-physiological systems such as the neurohumoral regulation of vital livings have been presented based on the extensively experimental and clinical evidences. As a consequence of these ontogenic and neurologic considerations, the adrenal medulla is commonly regarded to be a modified autonomic ganglion, and its pheochromocytes are looked upon as homolog of postanglionic neurons. The secretory activity of the adrenal medulla is so related to sympathetic innervation that these two are considered to be a functional unit *i.e.* sympathico-adrenomedullary system.

The sympathico-adrenomedullary system is, of course, one of the homeostatic regulator necessary to organism. When this system is activated by various stressors, such as muscle exercise, cold, emotional excitement, hypoglycemia and so on, the postganglionic neurons of the sympathetic nerves secrete noradrenaline, while the adrenal mdulla liberates adrenaline, a methylated derivative of noradrenaline.

In this report, muscle exercise and pain stimulus were adopted as non-specialized and physiological stressors and the dynamic aspects of homeostasis upon them were studied from the view-point of carbohydrate metabolism with special reference to the sympathico-adrenomedullary system.

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Objects of studies are first, homeostasis of blood sugar following muscle exercise on a bicycle ergometer as a neurohumoral regulation of carbohydrate metabolism, secondly the attitude or the physiological and biochemical significance of the sympathico-adrenomedullary system during muscular exercise, that is, the effect of the former upon the latter and vice versa and third, the afferent effects of adrenaline upon the central nervous system were studied.

EXPERIMENTAL MATERIALS AND METHODS

A muscle is a tissue that transforms chemical into mechanical energy, and when it contracts the potential energy is converted into motion at the expense of substances in the muscle itself. The general conclusions drawn from the investigations are that a muscle can provide large amounts of energy for a limited time in the absence of oxygen and that one source of this energy is the partial decomposition of glycogen into lactic acid.[72]

Actomyosin, which appears to be the true contractile protein of muscle, dissociates into actin and myosin attendant with muscle contraction; the energy of contraction is originated from the breakdown of ATP to ADP, which is catalysed ATP-ase. The resynthesis of ATP from ADP and phosphate is accomplished with the aid of energy obtained from muscle glycolysis.[73) 90) 91)] As muscle glycogen is consumed, pyruvic and lactic acid emerge as the principal end products, and the latter is seldom oxidized into the former, diffused into the blood stream and is thus carried to the liver where its utilization or resynthesis into glycogen and subsequent conversion to blood glucose may be accomplished. These biochemical analyses were first established by Cori,[20) 24)~28)] and this phenomenon is referred to as "Cori's lactic acid cycle". Muscle exercise, therefore, promotes the acceleration of dissimilation of muscle glycogen, which soon after getting resynthesized from blood sugar as an easily utilizable carbohydrate, it is apt to cause a fall of blood sugar level, unless homeostatic regulation occurs.

The homeostatic mechanism responsible for the precise regulation and control of carbohydrate metabolism acts successively through the integrated functions of the neurohumoral system, namely, the cerebrum, the diencephalon, the autonomic nervous system and the endocrine glands in order to maintain the blood sugar level not far from normal equilibrium. Thus, the maintenance of normal levels of sugar in the blood is one of the most finely regulated homeostatic mechanisms, and the liver plays an essential role. The liver (and to a meager extent the kidney) is the only source of sugar for the blood, while muscle, although it stores glycogen, does not contribute glucose to the blood. The unique position of the liver and the kidney as a source of glucose derived from the breakdown of glycogen is due to the presence in these organs of an enzyme, glucose-6-phosphatase, which enable to split glucose-6-phosphate to free glucose. The activity of the liver in maintaining normal levels of glucose in the blood is influenced by various hormones, including the following: insulin, anterior pituitary hormones, adrenocortical steroids, adrenomedullary catecholamines, glucagon and thyroid hormones. Insulin may inhibit hepatic pro-

duction of glucose and promote a reduction in the blood sugar by glycogenesis. The anterior pituitary hormones elevate the blood sugar by acting as antagonists of insulin. The adrenal corticosteroids stimulate gluconeogenesis and also serve insulin antagonists. Although the thyroid hormone should be considered as affecting the blood sugar, the effects of thyroid hormone on carbohydrate metabolism seem to be related to the general accelerating effects on metabolism. Adrenomedullary catecholamines and glucagon, the hormone of the alpha cells of the pancreas, are known respectively as hormones which raise the blood sugar by increasing hepatic glycogenolysis.

The biochemical background of the glycogenolytic action of adrenaline and glucagon has been gradually established by many investigators. Between 1928 and 1930, C. F. Cori and G. T. Gori[20)24)~28)] clearily established the glycogenolytic effect of adrenaline in the liver and muscle, with formation of glucose from the liver and lactic acid from muscle. They also demonstrated that the late hepatic glycogen accumulation which follows administration of relatively large doses of adrenaline to fasting animals is the result of accumulation of glycogen from lactate liberated by muscle. In 1937, C. F. Cori, Colowick and G. T. Cori[23)] demonstrated that glucose-1-phosphate (Cori's ester) is both the precursor of glycogen synthesis and the product of glycogenolysis, the interconversion being catalyzed by an enzyme phosphorylase. Then Sutherland and C. F. Cori (1951)[88)] reported that adrenaline and glucagon catalyze enzymatically the conversion of the liver phosphorylase from the inactive to the active form, while muscle phosphorylase fails to be activated by the latter hormone. This activation of phophorylase, both in the liver and in muscle, involves the synthesis of a cyclic adenine ribonucleotide.[78)89)] On the other hand Leloir and Cardini[66)] demonstrated that glycogen synthesis may actually occur by another pathway, with absence of phosphorylase. This pathway requires the presence of uridine-diphosphoglucose. Thus, there may well be two pathways for glycogen syntheses, and it is possible that they independently effect primarily glycogen syntheses (UDPG pathway) and glycogen breakdown (phosphorylase pathway). Summarizing these biochemical investigations on glycogenolysis, it can be stated that adrenaline reacts with tissue components to accelerate the formation of cyclic adenine ribonucleotide, which in turn accelerates the formation of active phosphorylase and this in turn alters the steady state of the uridine-diphosphoglucose and phosphorylase systems in favor of glycogenolysis, as shown in Fig. 1.[93)]

In this report, the physiological and biochemical connexion between the sympathico-adrenomedullary system and muscle exercise is dealt with from the standpoint previously described.

At first, in order to investigate the neurohumoral regulation as a whole upon the blood sugar level derived from physiologic and unspecialized changes of the internal environment, which causes carbohydrate metabolism, determination of the blood sugar level was carried on for three hours after muscle exercise on a bicycle ergometer, which could quantify the muscle work. Load was 4 kg for five minutes, and pedalling was sustained at the rate of one pedalling per second and thereabout. Blood sugar was determined by Hagedorn-

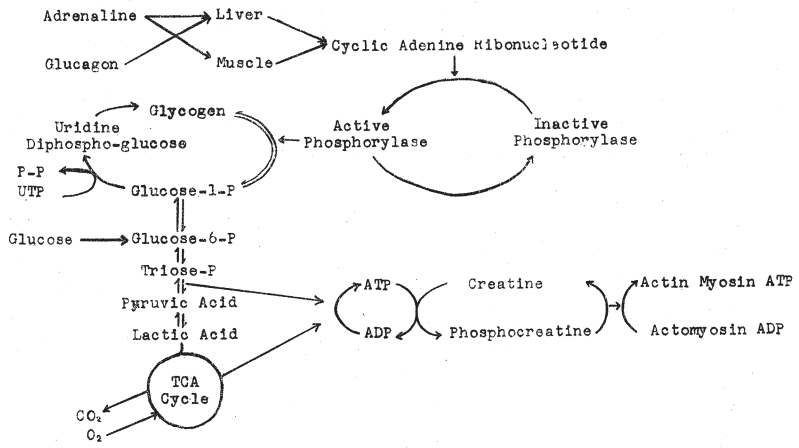

FIG. 1. Adrenaline and muscle glycolysis.

Jensen's iodometry[33)52)53)] at the preexercise resting state and every fifteen minutes for the first one hour and every 30 minutes for the following two hours after exercise in normal and healthy subjects of the third and fourth decades. They were forbidden the intake of food and water from the morning till the end of the examination. Cautions were also taken not to excite them emotionally and to keep them as calm and comfortable as possible, because both smoking[11)] and emotional excitement[39)40)] have been known to be causative factors influencing the blood sugar level. All experiments were started between 8 and 9 A.M. and completed within the subsequent three hours in order to eliminate the diurnal variation in blood sugar level, adrenaline secretion and other internal environmental factors.

Next, coming to the question whether the adrenomedullary secretion is augmented by the muscle work or not, the total amounts of free and acid-hydrolyzed urinary adrenaline and noradrenaline were determined every one hour for three hours after the muscle exercise and compared with that of the preexercise resting state. Concerning the sympathetic and adrenal mechanism of sugar mobilization in hypoglycemia, many investigations[15)34)] have been reported since Cannon, McIver and Bliss (1924),[18)] and Dill *et al.*[32)] reported that adrenaline actually increases glucose use during the period of exercise. In accordance with the assay of adrenaline and noradrenaline their endocrinological and pharmacological effects have been investigated in detail. Urinary adrenaline and noradrenaline were measured by Sano's improved method (1959)[82)83)] of the original trihydroxyindole fluorimetry by von Euler and Floding (1956)[46)] after acid-hydrolysis by twenty minutes boiling at pH 1–2 in the presence of conc. sulphuric acid. The urinary catecholamines were then adsorbed to alumina (aluminium oxide standardized, for chromatographic adsorption analysis, acc. to Brockmann. Merck Co. Ltd.) with ethylene-diamine-tetraacetic acid at pH 8.5. The eluate of alumina with 0.2 N acetic acid was adjusted to pH 6.5 and passed into the column-chromatogram of Amberlite-CG

50. After discarding the efluate and eluate of 0.2 M phosphate sodium buffer of pH 6.5, the eluate of 1 N hydrochloric acid was collected. By these procedures urinary adrenaline and noradrenaline can be collected selectively in the final eluate. The subsequent quantitative estimation of two amines in a mixture was based on the corresponding stabilized lutines oxidized at differential pH.[35) 45) 46) 47)] The values of excreted total adrenaline and noradrenaline were expressed as one hour excretion, but comparison with the preexercise excretion was generally not so accurate because of the time factor, so they were also calculated in terms of the values of per 100 mg of urinary creatinine. Urinary creatinine was assayed colorimetrically after Folin's method (1914).[48)]

Assuming that lactic acid is a regular intermediate or end products of carbohydrate metabolism of muscle through the Cori's lactic acid cycle,[27) 72)] its concentration in blood may be expected to increase when its formation is accelerated by work or by increase of adrenaline secretion.

The effects of adrenaline on muscle glycogenolysis and lactic acid formation have been demonstrated *in vivo*[8) 27)], and *in vitro*.[38) 58) 96) 97)] It increases the concentration of muscle phosphorylase from inactive to active and accelerates the breakdown of glycogen to hexose phosphate,[88)] but the glycogenolytic cycle may go to completion with the formation of lactic acid because of the lack of the phosphatase in muscle itself.[22)] It is also evident *in vivo* that adrenaline injection causes hyperlacticacidemia.[8) 28)] The lactic acid thus produced in muscle may in part be resynthesized to glycogen in situ at a later time, but majority of it diffuses into the blood stream from which it is largely removed up by the liver and replenished into glycogen or glucose, both liver and muscle glycogen—the former directly and the latter indirectly—contributing to the increase in blood sugar brought about by adrenaline.[21)]

Accordingly, in order to investigate the mutality between the blood sugar level, the excitement of the sympathico-adrenomedullary system and the lactic acid formation, simultaneous determination of serum lactate was also done by the colorimetry of Barker and Summerson (1941).[9)] In this paper, the author avoids the term "serum lactic acid", because it seems more appropriate to be treated as "lactate", since no substantial amount of free lactic acid can exist at the pH of body fluids.[77)]

In some normal subjects, the peripheral white blood cells (WBC) and the eosinophils were also counted prior to and every one hour after the muscle exercise, because these respective hematological elements are interpreted as one of the indicators of organic reactions. Many stimulating hypotheses are found in the previously published literatures concerning the relationship between stress and eosinopenia. It was Recant *et al.* (1950)[79)] who published extensive series of studies on eosinopenia induced by ACTH, cortisone, and adrenaline in man, and concluded that adrenaline could produce eosinopenia only in the presence of adrenals, pituitary and anterior hypothalamus, and that adrenaline acts indirectly to produce pituitary ACTH release, probably by affecting the hypothalamic controlling centers. Nevertheless, reevaluation is necessary of studies in which eosinopenia was the sole index of ACTH release: for example, Long,[68)] Brobeck and their collaborators[12)] showed in rats that the

one hour eosinophil fall to cold, insulin, laparotomy, or histamine was greatly reduced or abolished after adrenal demedullation although the four hour drop may persist,[68)71)] and also impaired or abolished by lesions of the brain or spinal cord which interrupt central sympathetic pathways.[12)] Of additional interest is the observation that the eosinopenia from intravenous ACTH tends to reach its maximum after three to four hours, while that from adrenaline is already the maximum after two hours, making it hardly possible that adrenaline eosinopenia is due to a subsequent ACTH release.[63)] The method used by the writer to count eosinophils was the direct one after Dunger's eosin-staining.

In order to inquire into the physiological significance of the sympathico-adrenomedullary system upon the muscle exercise, various sympathicolytic drugs were given prior to loading: these drugs used and the way of administration were as follows,

Chlorpromazine phenolphthalinate: perorally administrated, the daily doses were 25, 25, 50 and 50 mg respectively for the preceding four days and 25 mg was given in the early morning of the examining day.

Chlorpromazine hydrochloride: intramuscularly injected, 12.5 mg was given 30 minutes prior to the exercise.

2-Benzyl-imidazoline hydrochloride: intramuscularly injected, once dosis was 20 mg, given 5 to 20 minutes prior to the exercise.

Phentolamine methanesulfonate (Regitin®): intramuscularly injected, 10 mg was given in the same manner as benzyl-imidazoline.

Among these sympathicolytic agents, chlorpromazine has the sedative effectiveness to the central nervous system including diencephalon in comparison with the other phenothiazine derivative sympathicolytics, so the results obtained from the cases in which it was given to injection should be dealed under the special reference and consideration.

These results obtained from the case preliminarily treated with various sympathicolytics were compared with those from the very identical cases of non-pretreatment for evaluation of sympathico-adrenomedullary function at stress, through the blood sugar level, serum lactate level, urinary excretion of adrenaline and noradrenaline, and eosinopenic response.

Inquiring into the problem of this system as a homeostatic regulator, further studies were brought into clinically. The same experiments and measurements previously described were carried on in twenty-one cases with some autonomic or hormonal disorder. These included the diseases of the central nervous system such as internal hydrocephalus, craniopharyngioma, head trauma and grand-mal epilepsy: the diseases referred to the autonomic unbalance such as panvisceroptosis, Raynaud's disease and vegetosis; and other miscellaneous diseases, for example, anorexia nervosa, Behçet's disease, dermatomyositis and juvenile hypertension. As to the endocrine illness, the patients with diabetes mellitus, renal glycosuria and dystrophia adiposogenitalis were also examined.

Besides these efferent action of the sympathico-adrenomedullary system as previously mentioned, two kinds of catecholamines, especially adrenaline, have the certain afferent actions to the homeostatic regulating centers such as hypo-

thalamus and the pituitary gland directly or indirectly. Because there were many difficulties in methodology to examine these afferent actions of catecholamines accompanying with by muscle exercise, the author intended to observe the change of guinea-pig electrocorticogram followed by various cutaneous stimulations with the absence and presence of adrenaline and/or chlorpromazine injection.

EXPERIMENTAL RESULTS AND COMMENTS

1. Muscle Work and Blood Sugar Level

The blood sugar levels obtained in eight normal healthy subjects after muscle exercise on a bicycle ergometer are shown in Tab. 1, and Figs. 2 and 3. The blood sugar curves could be classified into two different patterns: the first pattern has following characteristics,

1. The preexercise blood sugar level at fasting state was from 70 to 90 mg/dl.

2. The blood sugar level was minimum immediately or 30 minutes after muscle exercise. The range of the drop from the preexercise level was from 6 to 16 mg/dl.

3. After the minimum state, it gradually increased, exceeding over the initial fasting level, reached the maximum value in a space of from 60 to 120 minutes.

4. Then, it decreased gradually and returned to the preexercise level about 180 minutes after the exercise.

It may be interpreted that the initial fall of the blood sugar is probably due to the glucose assimilation from blood to muscle and other organs against the increased carbohydrate dissimilation caused by muscle exercise, and that the following hyperglycemia is mainly due to the promoted liver glycolysis and partly due to the glucose replenished in the liver from serum lactate and pyruvate. The author names this response as "standard type" in this paper.

The second type observed in four normal subjects was characterized as follows,

1. Immediately after muscle exerise, the blood sugar level elevated slightly, the range

TABLE 1. The Blood Sugar Level Following Muscle Exercise on a Bicycle Ergometer in Eight Healthy Subjects.

Case (No.)	Age	Sex	before	0	15	30	45	60	90	120	150	180 min.	Type
												mg/dl	
2	34	♂	88	81	72	72		79		98		82	(I) Standard type
5	40	♂	82	75		81		93		88		77	
52	30	♀	72	66	68	73	75	77		84	79	72	
81	29	♂	87	84	78	75	84	85	89	78	80	75	
33	21	♀	65	67		65		65	67	73	65	69	(II) Stable type
71	21	♀	85	91	91	85	85	89	99	96	89	85	
72	27	♀	98	104	97	92	101	95	108	102	104	104	
80	25	♂	88	93	84	82	93	89	82	89	82	84	

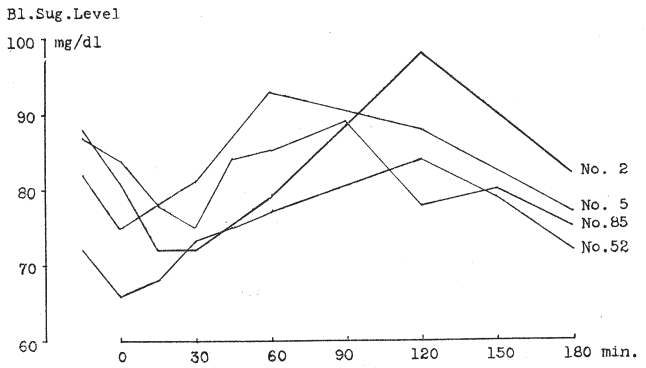

FIG. 2. Process of blood sugar level following muscle exercise. The Type I "Standard type".

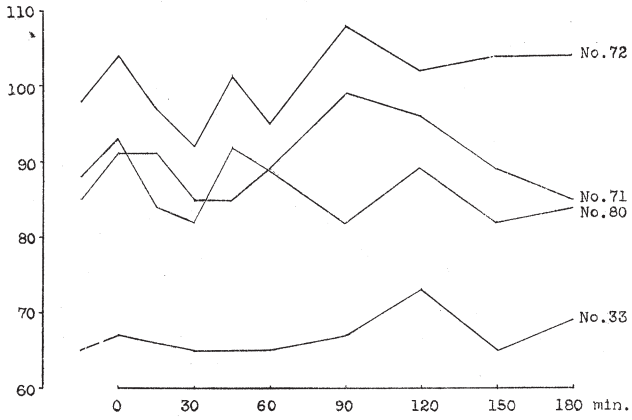

FIG. 3. Process of blood sugar level following muscle exercise. The Type II "Stable type".

being from 2 to 6 mg/dl.

2. The minimum level was from 30 to 45 minutes after the exercise.

3. Between 60 and 120 minutes after the loading, the blood sugar showed the maximum level, which in most cases exceeded the initial preexercise level.

4. The fluctuation of the blood sugar level after exercise was in less degree and stayed in the neighbourhood of the initial level.

In comparison with the former standard type, it could be pointed out that some differences existed between the two. The most striking point of the second type was the initial slight elevation prior to the hyperglycemic phase. Both the hypo- and hyper-glycemic levels were not so excessive, namely their deviations from the preexercise level were less than that of the standard type, therefore it seems that the second type is more stable to keep the blood sugar level than the first type.

In view of the postagressive oscillating reaction, the more divergently a response deviates from the homeostatic level, the more excessively subsequent response reverses. In the second groups, provided that the liver glycolysis is well-balanced enough to defeat the utilization of blood glucose which ensues from muscle work, the following oscillating reaction has to be lessened naturally. No definite fluctuation of the blood sugar level was observed in some cases. Although the cases existed in which no significant variation was detected in the blood sugar level throughout the examination of three hours duration after muscle exercise, the skeletal muscles when contracted get the energy through the breakdown of muscle glycogen and anabolize the blood glucose to muscle glycogen in resting state. For this reason, the stability of the blood sugar after muscle work may be accounted for the well-conditioned neurohumoral regulationship. Thus the stability is of importance physiologically in this type and it is treated in this paper as the "stable type".

The pattern of blood sugar curve is different among individuals of the normal healthy subjects, but the reproducibility exists evidently in anyone. (Fig. 4).

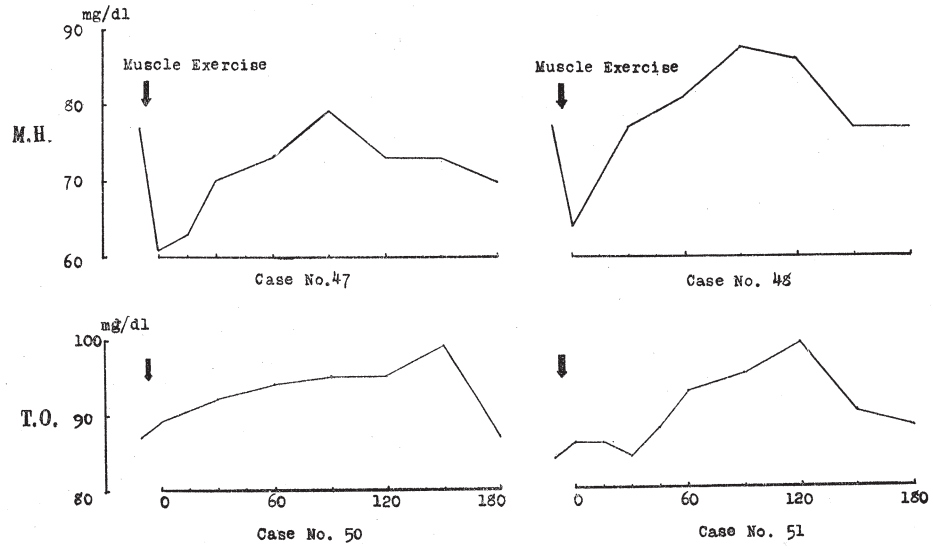

FIG. 4. Reproducibility of blood sugar process in the same subject following muscle exercise.

In contrast with these normal responses observed in healthy subjects, the postexercise blood glucose level was considerably metamorphosed in the subjects pretreated with various sympathicolytics previously described. These results are shown in Table 2. Cases No. 20, 21 and 24 pretreated with benzylimidazoline injection and Case No. 87 pretreated with chlorpromazine injection represented the maximal hyperglycemic phase just after and the minimal level 30 minutes after the exercise, followed by the relatively less fluctuated phase.

TABLE 2. The Blood Sugar Level Following Muscle Exercise on a Bicycle Ergometer in Eleven Healthy Subjects Pretreated with Various Sympathicolytic Agents.

Case (No.)	Age	Sex	Sympathicolytic agents	before	0	15	30	45	60	90	120	150	min. 180	Type
													mg/dl	
20	34	♂	Benzyl-imidazoline (I.M.)	74	81		65		72	70	70	74	72	(III) Hyper-glycemic type
21	23	♀		91	105		81		83	84	84	88	89	
24	37	♂		77	86		72		86		84		81	
87	26	♂	Chlorpromazine (I.M.)	78	93	86	86	78	75	78	75	69	78	
17	47	♂	Chlorpromazine (peroral)	98	88		83		81		79		84	(IV) Hypo-glycemic type
19	34	♂		84	84		73		77		79		77	
25	20	♂	Benzyl-imidazoline (I.M.)	91	82		81		82		75		79	
83	29	♂		83	62	62	63	69	62	62	62	71	71	
84	26	♂	Phentolamine (I.M.)	77	70	61	57		65		61		61	
18	23	♂	Chlorpromazine (peroral)	86	75		82		91		90		107	(V) Labile type
86	25	♂	Chlorpromazine (I.M.)	88	103	81	94	96	105	94	96	92	81	
12	40	♂	Benzyl-imidazoline (I.M.)	non muscle exercise	89		87		94		91		91	
13	34	♂			87		84		84		97		86	
14	36	♂			89		87		94		93		94	

The characteristic feature in these four cases was the abrupt and unusual elevation of the blood sugar level just after the work with subsequent less fluctuation, therefore this pattern induced by sympathicolytics was named here as "hyperglycemic type" (Fig. 5).

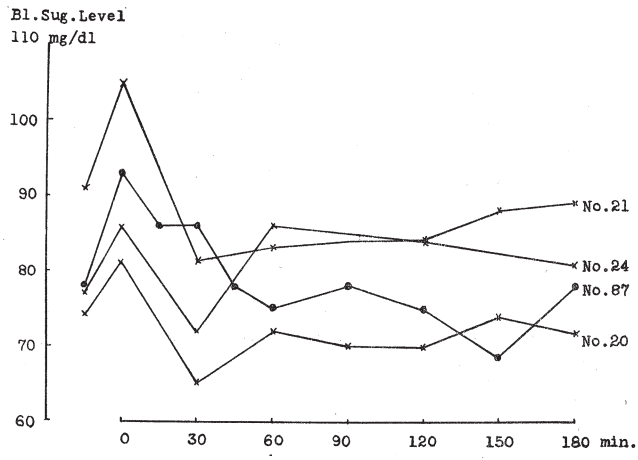

FIG. 5. Process of blood sugar level following muscle exercise in the subjects pretreated with sympathicolytics. The Type III "Hyperglycemic type".

The second type observed in the subjects pretreated with sympathicolytics was most interesting in relation to the adrenomedullary function. In this type, the initial level prior to injection of sympathicolytics was highest for the whole three hours examination. That is to say, after the muscle exercise the blood sugar levels decreased gradually and brought out neither a definite hyperglycemia nor a significant fluctuation, the blood sugar level after the exercise being generally below the normal concentration. So they were treated here under the name of "hypoglycemic type". Though no distinct difference was observed among three sympathicolytics used in the interfering effect against the blood sugar rising, the phentolamine-treated case (No. 84) was most affected, and the minimal level was even 57 mg/dl, but no hypoglycemic syndrome appeared (Fig. 6).

The third type occurred only in two cases (No. 18 and 86), who had been given chlorpromazine perorally and intramuscularly respectively, and the post-exercise oscillation in the blood sugar level was so aggravated that the hyperglycemia and hypoglycemia appeard with alternate regularity or irregularly (Fig. 7). This is the consequence of actions that chlorpromazine affected not only the sympathico-adrenomedullary system but also it might operate upon the homeostatic regulartory center such as hypothalamus. Chlorpromazine is known as a more affinitive drug than other sympathicolytics to hypothalamus and may ensue the interfered homeostasis in somebody.

The affection of the sympathicolytics themselves upon the blood sugar level

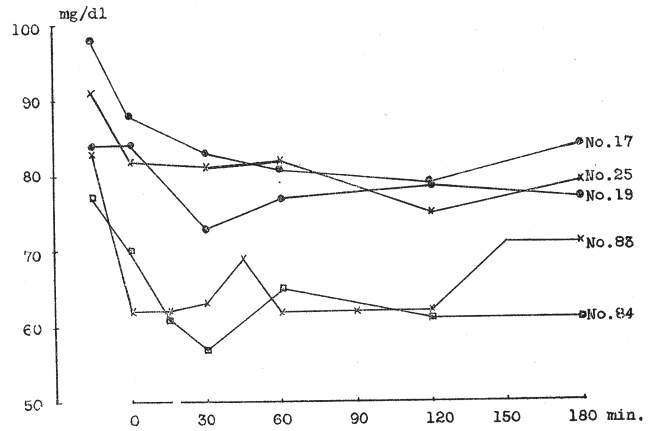

FIG. 6. Process of blood sugar level following muscle exercise in the subjects pretreated with sympathicolytics. The Type IV. "Hypoglycemic type".

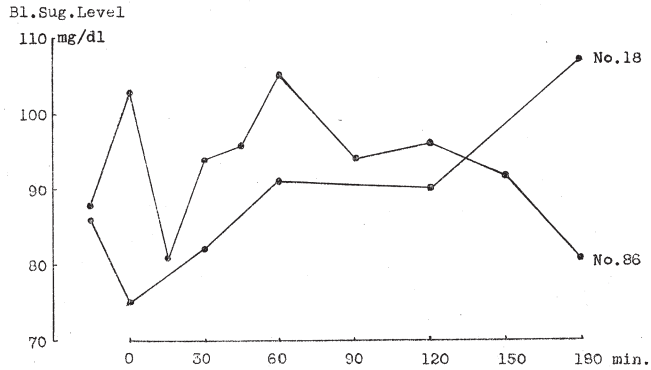

FIG. 7. Process of blood sugar level following muscle exercise in the subjects pretreated with sympathicolytics. The type VA and VB "Labile type A and B".

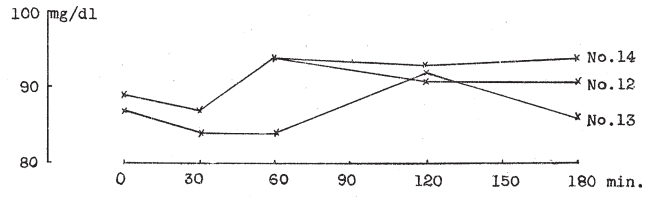

FIG. 8. Process of blood sugar level following Benzyl-imidazoline injection in normal resting subjects.

was examined as the fundamental matter, they, however, could singly induce neither hypo- nor hyper-glycemia in three resting healthy subjects (Cases No. 12, 13 and 14) (Fig. 8).

The six types of blood sugar pattern are schematically illustrated in Fig. 9; I and II in normal subjects without pretreatment and III, IV and V in normal subjects treated with various sympathicolytics.

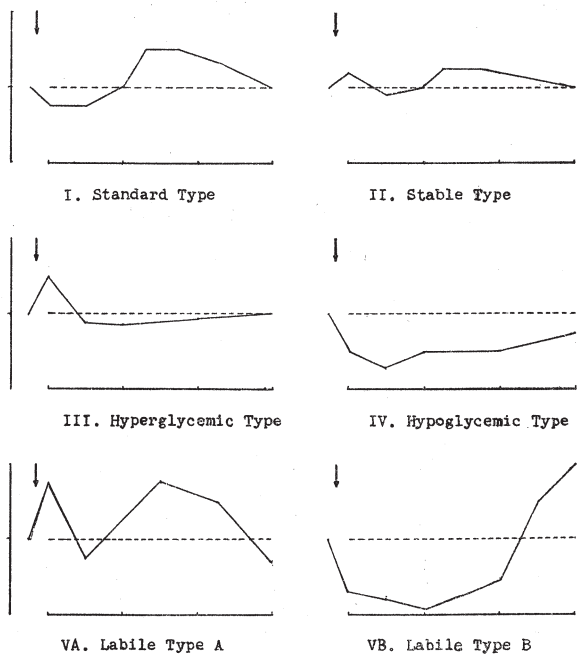

FIG. 9. Schema of various types of blood sugar levels following muscle exercise in normal subjects without pretreatment (I and II) and pretreated subjects with sympathicolytics (III, IV, VA and VB).

The measurements of blood sugar were also brought in the same way into twenty-one patients with nervous disease, *e.g.* internal hydrocephalus (Case No. 69), head trauma (No. 75), craniopharyngioma (No. 79) and grand-mal epilepsy (No. 55); endocrine disease, *e.g.* diabetes mellitus (No. 46), Frölich's syndrome (No. 62) and anorexia nervosa (No. 49 and 54); and other miscellaneous diseases such as renal glycosuria (No. 57), juvenile hypertension (No. 10), visceroptosis (Nos. 1, 3, 72 and 74) and dermatomyositis, a kind of collagen disease with muscle degeneration (Nos. 60 and 76).

The normal response was observed only in two patients: type I (standard type) in one case with renal glycosuria and type II (stable type) in another with visceroptosis. The remaining majority is almost identical with pathological types III, IV and V. They consisted of six cases with type III, seven

TABLE 3. The Blood Sugar Level Following Muscle Exercise on a Bicycle Ergometer in Twenty-One Cases with Neurohumoral Disorders

Case (No.)	Age	Sex	Clinical diagnosis	Before	0	15	30	45	60	90	120	150	min 180	Type
													mg/dl	
57	38	♂	Renal glycosuria	100	90	92	95	92	101	101	25	89	89	I
72	27	♀	Visceroptosis	98	104	97	92	101	95	108	102	104	104	II
1	21	♂	Visceroptosis	88	97		93		93		75		72	
10	20	♂	Juvenile hypertension	88	91		98		83		74		83	
55	32	♂	Grand-mal epilepsy	82	87	88	83	79	79	72	74	78	85	III
62	34	♂	Frölich's syndrome	67	70	76	83	67	65	74	76	76	69	
75	36	♂	Head trauma	110	116	118	97	96	90	99	108	99	111	
76	26	♂	Dermatomyositis	80	120	94	83	101	81	87	90	88	74	
65	32	♂	Behçet's syndrome	106	99	94	82	80	80	78	80	87	84	IV
3	32	♂	Visceroptosis	93			98		89		79		116	
15	29	♀	Raynaud's syndrome	83	93		78		98		78		84	
46	45	♂	Diabetes mellitus	126	96		95	98	77	86	80	100	69	
54	26	♀	Anorexia nervosa	69	101	98	73	89	95	73	93	86	87	VA
69	24	♂	Internal hydrocephalus	109	144	117	117	107	119	126	108	107	95	
74	18	♂	Visceroptosis	115	119	124	132	134	113	125	119	115	145	
79	49	♂	Craniopharyngioma	94	85	91	80	91	99	84	77	80	80	
7	38	♂	Pulmonary tuberculosis	100	79		79		111		102		105	
49	21	♂	Anorexia nervosa	85	76	64	64	59	52	59	50	61	84	
58	30	♂	Vegetosis	68	74	68	68	68	77	67	79	89	96	VB
60	26	♂	Dermatomyositis	115	126	122	115	113	110		101	73	56	
85	27	♂	Vegetosis	79	76	74	67	83	85	79	85	81	100	

cases with type VA, five cases with type VB, and only one case with type IV. From these observations, it may be evident that some dysfunction took place in these subjects to prevent from sustaining the blood sugar homeostasis. The pattern of blood sugar level was independent on clinical entity, for example there were two or more patterns in the same clinical entity such as viscero-ptosis or anorexia nervosa.

Accordingly, the analysis of blood sugar curve following the muscle exercise is available for diagnostic test to examine its orderly regulation.

2. Muscle Exercise and the Urinary Excretion of Adrenaline and Noradrenaline

It is apparent in the experiments above described that the blood sugar level after muscle work is more or less affected or interfered by the sympathicolytic drugs and its native reaction is modified. From these experiments the sympathico-adrenomedullary system must be considered to contribute in some way to the homeostatic regulation of the blood sugar.

In recent decade, the increase of urinary excretion of both adrenaline and noradrenaline after muscle work has been confirmed by many investigators such as von Euler and Hellner (1952)[44], Kärki (1956)[65] and Elmadjian (1951[41], 1958[39]).

In this paper the urinary excretion of adrenaline and noradrenaline was examined in order to compare the cases pretreated with various sympathicolytics injections with the cases devoid of such injections. These are shown in Table 4, and Fig. 10.

In intact normal subjects (Cases Nos. 80 and 81) both catecholamines excretion into urine were augmented by muscle work with the prominent rise

TABLE 4. Urinay Excretion of Adrenaline and Noradrenaline Before and After Muscle Exercise on a Bicycle Ergometer in Three Normal Subjects.

Case (No.)		Pretreatment		Before	1st One-Hour	2nd One-Hour	3rd One-Hour
T.T. 25 y.o. ♂	80	Non-pretreatment	A	0.38(1.06)	0.76(2.09)	0.41(0.74)	0.36(0.71)
			NA	0.74(2.04)	2.54(6.97)	0.76(1.37)	0.52(1.02)
	86	Chlorpromazine (I.M.)	A	0.63(0.83)	0.59(1.13)	0.15(0.25)	0.17(0.32)
			NA	1.83(3.46)	1.09(2.09)	2.06(3.35)	1.73(3.25)
A.T. 29 y.o. ♂	81	Non-pretreatment	A	1.53(0.83)	0.71(1.18)	0.17(0.25)	0.55(1.31)
			NA	1.49(0.81)	0.79(1.31)	0.74(1.01)	0.49(1.16)
	83	Benzylimidazoline (I.M.)	A	0.75(0.54)	0.33(0.29)	0.07(0.14)	0.65(0.79)
			NA	0.76(0.61)	0.63(0.55)	0.34(0.72)	0.65(0.79)
S.T. 26 y.o. ♂	84	Phentolamin (I.M.)	A	0.20(0.53)	0.04(0.06)	0.18(0.42)	0.13(0.28)
			NA	0.96(2.54)	1.26(2.03)	0.98(2.27)	0.19(3.86)
	87	Chlorpromazine (I.M.)	A	0.24(0.95)	0.26(0.26)	0.27(0.55)	0.15(0.29)
			NA	1.09(4.37)	1.41(1.43)	0.99(2.03)	0.63(1.25)

Both catecholamines are measured as total value after acid-hydrolysis, expressed as microgram and in parentheses calculated as microgram per 100 mg of urinary creatinine.

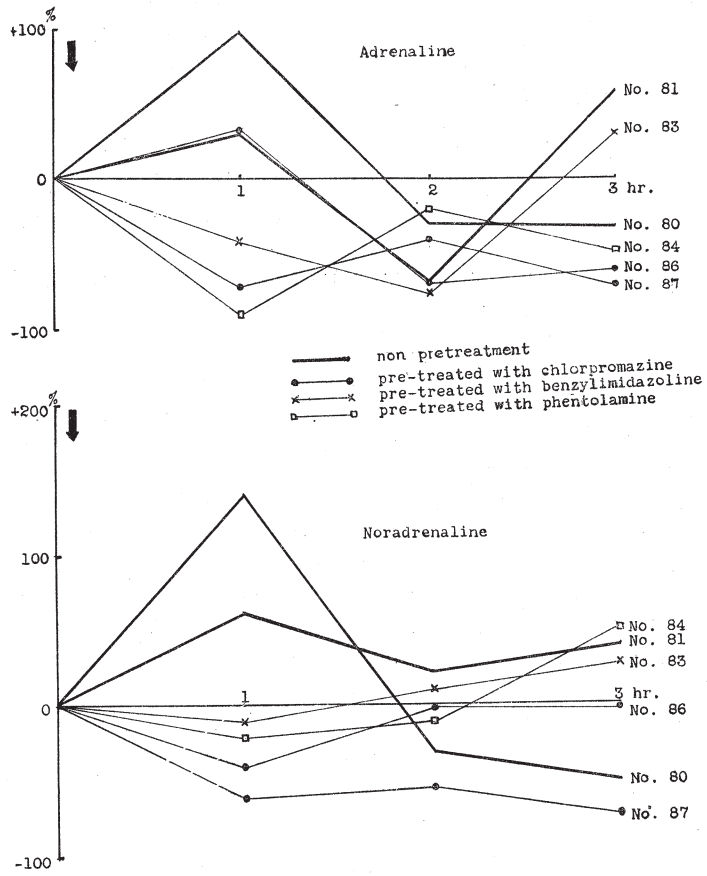

FIG. 10. Percentage variation of urinary adrenaline and noradrenaline excretion following muscle exercise in the subiects Pre-treated with nothing (——) and various sympathicolytics injection (——).

in the first one hour urine, and no time discrepancy was detected in the excretory increase between two catecholamines (Cases Nos. 80 and 81).

In general, adrenaline elevation was of less degree than noradrenaline in these particular experiments, there is, however, a divergence of opinion on the excretory ratio between noradrenaline and adrenaline: for instance, von Euler and Hellner (1952)[44] reported that urinary output of catecholamines was 0.03–0.07 μg/min. in rest and 0.05 μg/min. during heavy muscular work (viz. 1.5 km running or 10 km ski run competition) in young healthy subjects and that the percentage of adrenaline in the excess output was generally not changed from the normal. Elmadjian, Hope and Lamson (1958)[39] studied the variations in the excretion pattern of noradrenaline and adrenaline during the stress, observed varying degrees of elevated noradrenaline excretion with normal or slightly elevated adrenaline in hockey players during a moderately tense game, but as

there was elevated adrenaline excretion with no increases in noradrenaline in pursuitmeter experiments, they finally suggested that when an intense emotional display was evident, such as in hockey palyers, amateur boxers, both noradrenaline and adrenaline were elevated.

What is disputable why the variety of these observations occurs lies in what is the very urinry catecholamines. Both adrenaline and noradrenaline are excreted into urine not only in free form[85] but also in phenolic sulphate form,[47] glucuronides form,[19] 3-methoxy-4-hydroxyphenyl form (metanephrine and normetanephrine)[2,3,4,5,6] and other unidentified form, so the determination of only the amount of free plus acid-hydrolysed form may not signify the true nature of adrenal and sympathetic activation. Preliminary hydrolysis of the urine at pH 1–1.5 for 20 minutes ensures the inclusion of the phenolic sulphate fraction of conjugated catecholamines in the estimate, glucuronides are, however, not hydrolysed under these conditions. But the partial determination may also indicate some aspect of the true nature so long as the metabolic rout of these catecholamines might not undergo intense alternation. For the reasons above described, it may be referred to the consequence of activation of the sympathico-adrenomedullary system when the urinary output of even the only free and acid-hydrolizable fraction of catecholamines increases as a matter of fact.

Inquiring into the urinary output of catecholamines in reference to the sympathico-adrenomedullary function, further experiments were conducted into the same healthy subjects. These consisted of the combination of the preliminary injection of various sympathicolytics and muscle work, and the subsequent affection of urinary catecholamines was pursued in each one hour fraction. In the cases pretreated with any sympathicolytics injection the urinary excretion was remarkably affected, viz. the ordinary increase of excretion disappeared or the depression of excretion was observed, which was more prominent in the first one hour excretion but lasted in some cases (Nos. 86 and 87) till the end of experiments. Postexercise elevation of the urinary output was more predominant in adrenaline than in noradrenaline though the latter was also affected.

In two intact subjects, urinary adrenaline increased from 1.06 to 2.09 (Case No. 80) and from 0.83 to 1.18 (Case No. 81) by muscle work, but in the same chlorpromazine counteracted the postexercise elevation and caused the decrease (No. 86) of adrenaline excretion from 0.83 to 0.25 in the second one hour urine and to 0.32 in the third. (The values are expressed in terms of microgram per 100 mg of urinary creatinine excretion.)

Three sympathicolytic drugs used had the effectiveness in this respect, but qualitative differences were observed among them, for instance phentolamine was likely to have the most strong action in depressing degree of adrenaline output, and chlorpromazine was the most long-acting.

Noradrenaline output into urine was less changed by these drugs except for Case No. 87 than that of adrenaline. This discrepancy between the two catecholamines is likely to mean that the cardiovascular balance is more stable than the endocrinological one when these drugs are given, the former being much related to noradrenaline and the latter with adrenaline.

Subjectively, the muscle fatigability after work was seriously aggravated in the pretreated cases especially in chlorpromazine treated subjects (Nos. 86 and 87) and also, though transient, in phentolamine-treated subject (No. 84). As already described, adrenaline has the biochemical relationship with the transformation of inactive muscle phosphorylase to active form to prevent the complete disappearance of this enzyme in a fatigued muscle and to accelerate the resynthesis of active phosphorylase during recovery from fatigue.[29]

In the field of physiology, the noteworthy finding by Orbeli that when the response of a nerve-muscle preparation is diminishing because of fatigue stimulation of the sympathetic increases the height of the contractions has attracted attention as Orbeli's phenomenon, and in the field of clinical medicine, it is well known that after the injection of adrenaline skeletal muscle becomes fatigued at a slower rate than usual. The observation in my own experiments that the cases where the sympathico-adrenomedullary system had been blocked with sympathicolytic agents were more easily fatigued is referable to these biochemical, physiological and clinical evidences, and thus it becomes definite that the adrenaline has the endocrinological importance during a period of work.

3. Muscle Work and Its Affection upon the Peripheral Blood Cells

It is practical and important to measure the peripheral WBC and eosinophil count after exposure to various stress whether the stressor is sufficient and whether the subject reacts to the stressor.

Already, in 1924 Isaacs and Gordon[64] reported that running produced the increase in the number of WBC and the decrease of eosinophils. Adrenaline and noradrenaline are known as capable to produce leukocytosis and eosinopenia.[54]

In my own experiments, two normal young subjects showed the definite increase of WBC and the definite decrease of eosinophils after muscle exercise on a bicycle ergometer for five minutes (Table 5). This means that the muscle exercise is significant enough as a stressor. The initial count of WBC was 5200 and 5500 (Cases Nos. 80 and 81), and the proportionate elevation with regularity was recognized in both cases three hours after exercise, the former elevating 71.3% and the latter 44.1% three hours later.

Eosinopenic response was also observed in these two subjects, but it was so abrupt that the minimal value was during the first one hour after exercise in contrast to the gradual and proportional increase of WBC.

Although these hematological affections were induced in four pretreated cases with various sympathicolytic drugs (Cases Nos. 83, 84, 86 and 87), the irrugularity of leukocytosis and eosinopenia appeared in three cases and almost depressed response of leukocytosis and delayed response of eosinopenia were produced only in the last case (No. 87).

The physiological significance concerning with these hematological affection after muscle exercise has been studied from various angles[1)92)] but it still remains much disputable. About ten years ago, the predominating hypotheses were that the pituitary ACTH and consequent adrenal 11-oxysteroids might

TABLE 5. Percentage Variation of Peripheral WBC and Eosinophils Count after Muscle Exercise on a Bicycle Ergometer

Case (No.)	Age	Sex	Clinical diagnosis (Pretreatment with sympathicolytic agent)	WBC				Eosinophils			
				Initial count /mm³	1 hr (%)	2 hr (%)	3 hr (%)	Initial count /mm³	1 hr (%)	2 hr (%)	3 hr (%)
80	25	♂	Normal	5 200	+27.2	+31.5	**+71.3**	73	**−70.2**	−60.9	−56.6
81	29	♂	(Non-pretreatment)	5 500	+18.2	+36.4	**+44.1**	46	**−54.0**	−31.4	−17.8
82	33	♂	Moderately advanced pulmonary fibrosis (Hamman-Rich)	7 000	**+94.5**	+53.0	+46.5	100	−33.3	−27.7	**−58.3**
85	26	♂	Vegetosis	5 800	+12.1	+31.0	**+48.3**	18	**−33.3**	+11.1	+11.1
48	14	♂	Pituitary dwarfism	8 100	**+13.6**	− 6.2	+ 8.6	175	**−25.2**	+14.3	+ 7.1
79	40	♂	Pituitary chromophobe adenoma	8 300	+ 8.4	+38.6	**+72.2**	381	**−15.5**	+65.5	− 1.6
83	29	♂	Benzyl-imidazoline (I.M.)	5 500	**+50.9**	−30.9	−14.5	67	−31.3	− 3.1	**−43.8**
84	26	♂	Phentolamine (I.M.)	6 100	+55.6	+28.8	**+94.0**	220	−34.2	−16.7	**−34.8**
86	25	♂	Chlorpromazine (I.M.)	6 100	−16.8	**+29.5**	− 8.2	150	−20.0	**−24.0**	**−24.0**
87	26	♂	Chlorpromazine (I.M.)	6 800	+ 3.0	− 8.0	+ **5.6**	125	+30.0	+15.0	**−30.0**

The initial count is shown as absolute value, and the following count as percentage variation. Maximal value in WBC and minimal value in eosinophils are in Gothic.

cause these affections in response to stress and that it was adrenaline that served as an activator upon the hypophyseo-adrenocortical system. For example, Recant *et al.*[79] reported that adrenaline could produce eosinopenia only in the presence of adrenals, pituitary and anterior hypothalamus, and concluded that adrenaline acted indirectly to produce pituitary ACTH release, probably by affecting the hypothalamic controlling centres. Now-a-days, however, it is conceived that adrenaline-induced eosinopenia needs not the activation of the pituitary-adrenal axis,[75] because many investigators revealed that administration of adrenaline in adequate dosage intravenously or subcutaneously to man generally fails to increase either the plasma or urinary corticosteroids, even though producing a marked eosinopenia.[42][64] As previously mentioned, reevaluation is necessary of these physiology; it must be considered that there exists time discrepancy among these esinopenia induced by adrenaline, ACTH or various stressful conditions. For example, the eosinopenia from intravenous ACTH tends to reach its maximum after 3 to 4 hours, while that from adrenaline is already the maximum in 2 hours, and exposure to cold and laparotomy causes the fall even one hour.[68][71]

The incipient fall of eosinophils after muscle work was observed in two normal cases (Nos. 80 and 81) and this was also detected even in the patients with hypotituitarism: pituitary dwarfism of 14 age (No. 48) and pituitary adenoma of 40 age (Case No. 79). The time discrepancy of eosinopenic response between ACTH infusion test and somo stressful conditions such as cold, fear and muscle work and the presence even in these patients with hypo-

pituitarism make it extreme unlikely that the eoisnopenic response of early stadium after muscle work is due solely to a subsequent ACTH release.

In sympathicolytics-treated cases, the incipient fall of eosinophils was not significantly but slightly affected, although the urinary catecholamines were considerably altered. And the persistence of incipient eosinopenic response after muscle work even in hypopituitarism and in pharmacological interruption of sympathico-adrenomedullary system may indicate that neither ACTH and nor adrenaline alone can ensure sufficiently the one hour eosinopenia after work, though both of the two hormones may be concerned only in some degree. The three hour eosinopenia was abnormal in three cases (Nos. 85, 48 and 79), vegetosis, pituitary dwarfism and pituitary adenoma respectively, so it is more preferable that the pituitary is much concerned in three hour response than the adrenal medullae.

Chlorpromazine was also the most effective in the interruption of these hematological reactions among the sympathicolytic drugs adopted.

4. Serum Lactate Level after Muscle Exercise

As already described, muscle exercise produces the rise of blood lactate level. During a period of working, muscle are deriving energy from more anaerobic glycolysis and after exercise the oxygen consumption does not immediately return to the resting level, then in the state of adequate oxygen supply occurs the oxidative recovery which is associated with the removal of lactate and the refilling of the energy stores (resynthesis of phosphocreatine and formation of glycogen from blood sugar and lactate).

The results of serum lactate level after the muscle exercise on a bicycle ergometer for five minutes are summarized as follows (Table 6, Fig. 11). In normal subjects without any pretreatment (Nos. 80 and 81), the levels rose immediately after the work but the recovery to the initial levels was observed 15 minutes thereafter. The influence on lactate production at relative oxygen insufficiency was examined in a patient of moderately advanced pulmonary

TABLE 6. Percentage Variation of the Serum Lactate Level Following Muscle Exercise on a Bicycle Ergometer, and the Affection of Various Sympathicolytic Agents upon It

Case (No.)	Age	Sex	Clinical diagnosis (Pretreatment)	Before (mg/dl)	Percentage variation 0	15	30	45	60	120	min 180
80	25	♂	(Non-pretreatment)	23.3	+ 80	+ 3	+ 1	0	0		
81	29	♂	(Normal	31.3	+ 78	+ 1	− 1	0	0		
83	29	♂	Benzyl-imidazoline	25.9	+ 43	− 2	− 2	− 2	− 1		
84	26	♂	Phentolamine	27.6	+126		+ 26	+ 7	+ 3		
86	25	♂	Chlorpromazine	25.7	+413	+342	+154	+43	+19		
87	26	♂	Chlorpromazine	27.9	+207	+ 76	+ 72	+70	+32		
82	33	♂	Pulmonary fibrosis (Hamman-Rich)	27.4	+154	+ 91	+ 23	+ 1	+ 1	+ 2	0
85	26	♂	Vegetosis	28.4	+ 88	+ 76	+ 30	+30	+ 9	− 3	

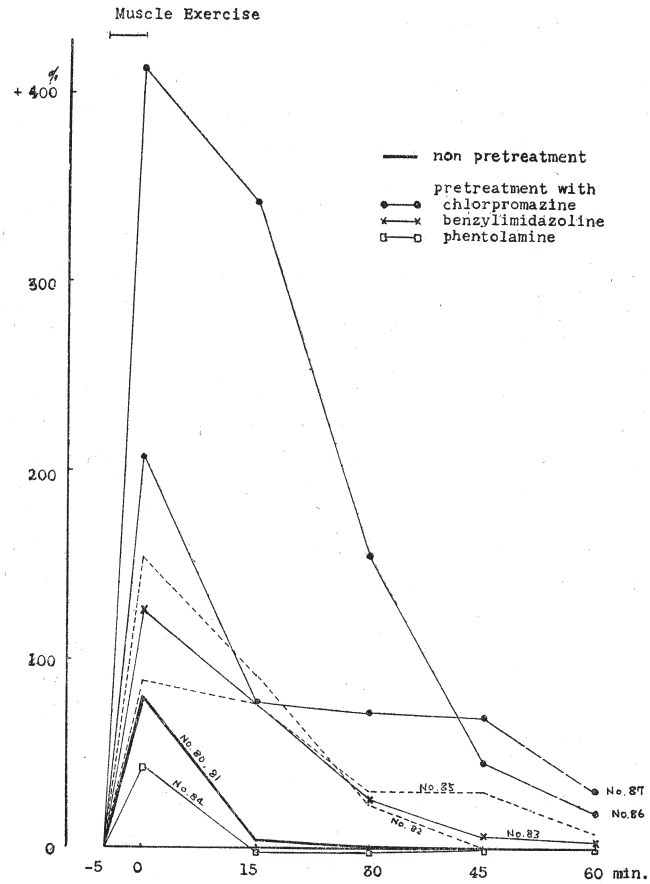

FIG. 11. Percentage variation of serum lactate level following muscle exercise in the subjects pre-treated with nothing and various sympathicolytics.

fibrosis (No. 32 who was diagnosed clinically as "chronic Hamman-Rich's syndrome"): the lactate level immediately after work was higher than the healthy subjects and the recovery to the initial level was delayed. In this experiment, it may be revealed that anaerobic state was somewhat overwhelming than aerobic state.

In four subjects pretreated with various sympathicolytics, two different patterns were obtained. First, in No. 83 preliminarily injected with benzylimidazoline, the rise immediately there after was in less degree and the recovery occurred within 15 minutes. Second group was characterized as that the level immediately after was much higher and the recovery was much prolonged than the normal.

These results may be apparently contradictory and illogical. Here we must realise that the elevation of serum lactate level serves as an indicator that

muscle work ensures the lactic acid production. For during recovery period, the lactate is oxidized to pyruvate and the concomitant disappearance of lactate from blood is proceeding.

The phosphorylase activity is somehow implicated in adrenaline, and muscle work is one of the activator on the sympathico-adrenomedullary system: consequently, the lactate level relates also to adrenaline. In four subjects pretreated with sympathicolytics, the usual elevation of urinary catecholamines after work was suppressed and also the phosphorylase activity seemed to be suppressed correspondingly in these cases, so it might be preferable to interpret that the suppression of lactate level elevation was due to the interfered activation of muscle phosphorylase and the prolongation of its recovery was due to the interfered activation of liver phosphorylase. The phosphorylase activity is reversible, so adrenaline has the effectiveness upon one step of glycogen resyntheses in the liver and in muscle. The delay of recovery is most prominent in chlorpromazine treated cases (Nos. 86 and 87), implying that chlorpromazine is so long-active and affinitive to the liver that liver phosphorylase concerned with the successive reactions from lactate to glycogen is more affected than muscle phosphorylase.

The delay of lactate level recovery is also observed in the patients of vegetosis in which the ordinary excess output of urinary catecholamines was of less degree.

It may not be appropriate to take a view that adrenaline has also a connexion with serum lactate level through both glycogenolysis (lactic acid production) and resynthesis of glycogen and glucose from serum lactate by the medium of muscles and liver phosphorylase activity.

5. The Afferent Effect of Adrenaline

Thus far, the intentions and considerations of my own experiments have been brought into the focus such as the activation of sympathico-adrenomedullary system under certain stress conditions, through the urinary excretion of catecholamines and the circulating blood cell count, and the endocrinological affections of adrenaline upon the lactate production in striated muscles and its removal by the liver under muscle exercise and upon the regulation of blood sugar homeostasis.

On the other hand, adrenaline has the remarkable centripetal effects besides the somatic actions, as it is well known clinically that headache, excitement, tenseness, exhilaration, restlessness, anxiety, agitation, fear and even hallucination appear after 0.5 to 1.5 mg intramuscularly or subcutaneously injection of adrenaline in man.

The following experiments were accordingly made. While it is beyond the scope of my own experiments to take up the effects of adrenaline itself upon the central nervous system, the subjects in this paper were restricted to whether or how adrenaline modifies the central evoked potential induced by any stressful condition at the cutaneous sensory receptors. Inquiring into these subiects, the author adopted the electrophysiological experiments on adult guinea-pig.

The guinea-pig was preliminarily narcotized with urethan intraperitoneal injection, trepanned with the utmost care not to injure the brain, and then six silver ball electrodes of less 0.5 mm in diameter were placed on the cortical surface, *i.e.* frontal and sensory areas three for each.[76] The affection of adrenaline was observed through the changes of electrocorticogram induced by cutaneous stimulation of hind legs, which consisted from various modalities such as tactile, pressure, cold and pain. In these cutaneous stimulation, pain is known as one of stressor and also it has been investigated in recent times that the frontal area is more implicated as an autonomic, homeostatic regulating center in the vital response. So it was significant to compare the degree of affection on the electrocorticogram between these two groups of electrodes and between the pain stimulus and the others, and to compare them with the records between these stimulations only and the further additional administration of adrenaline or chlorpromazine. Electrocorticogram was recorded after complete narcosis with urethan and successively after the intramuscular injection of 0.1 mg of adrenaline hydrochloride or 0.5 mg of chlorpromazine hydrochloride.

The records of both frontal area and sensory area without any stimulation under nontreatment of adrenaline and chlorpromazine were rapid and small waves with certain irrugularity. These waves were excited by some cutaneous stimulation, and the most prominent excitement was caused by both pain and cold stimulation as expected. There can be detected no distinct difference between the two group records of frontal and sensory areae.

About 10 minutes after adrenaline injection, spontaneous discharge from cerebral cortex was slightly affected to be more rapid and small, and at this period pain and cold stimulations intensified these changes, which were more definite in the record of frontal area. Pressure and tactile stimulation was less affective (Fig. 12).

It is of utmost interest that the augmentation of the cortical evoked potential of both pain and cold stimulation by adrenaline was completely nulified in the corticogram of guinea-pig pretreated with chlorpromazine. About 60 to 120 minutes after its injection, stressful stimuli such as cold or pain failed to excite the frontal record at all (Fig. 13).

Though obscure and disputable concerning to the augmentation of nerve transmission by catecholamines, it is no doubt that adrenaline has the augmentative action of afferent excitement, of which nature deserves to stressful such as cold and pain. Bülbring and Burn,[13] Marrazzi[70] and Malkéjac[69] also observed an increase of nerve response following suitable doses of adrenaline. They believed that adrenaline may normally play a helpful role in stressful situations and that adrenaline will enhance condition in peripheral nerves under certain conditions.

In addition to these indirect augmentative action of adrenaline, it may still remain to reinvestigate the direct effectiveness of adrenaline to the central nervous system especially to hypothalamic center. Because, in spite of previous observation that adrenaline failes to pass the blood-brain-barrier at all, the work currently in progress using tritium-labeled adrenaline suggestes that

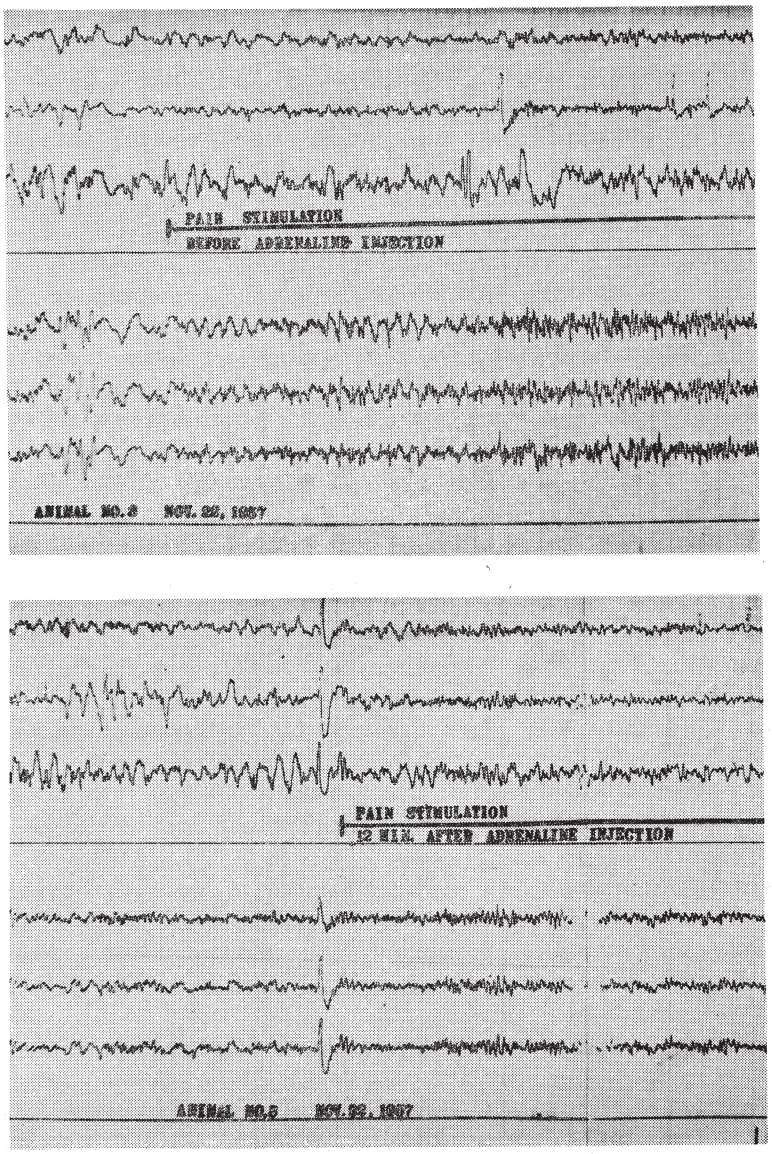

FIG. 12. Affection of adrenaline upon the electrocorticogram of adult guinea-pig under the cutaneous pain stimulation. Upper three records are taken from sensory area; lower three from frontal area.

there are regional differences in the blood-brain-barrier to adrenaline, so that measurable amounts may enter the hypothalamus.[80]

6. Miscellaneous Somatic Changes Associated with Muscle Exercise

The somatic changes after the muscle exercise except for previously

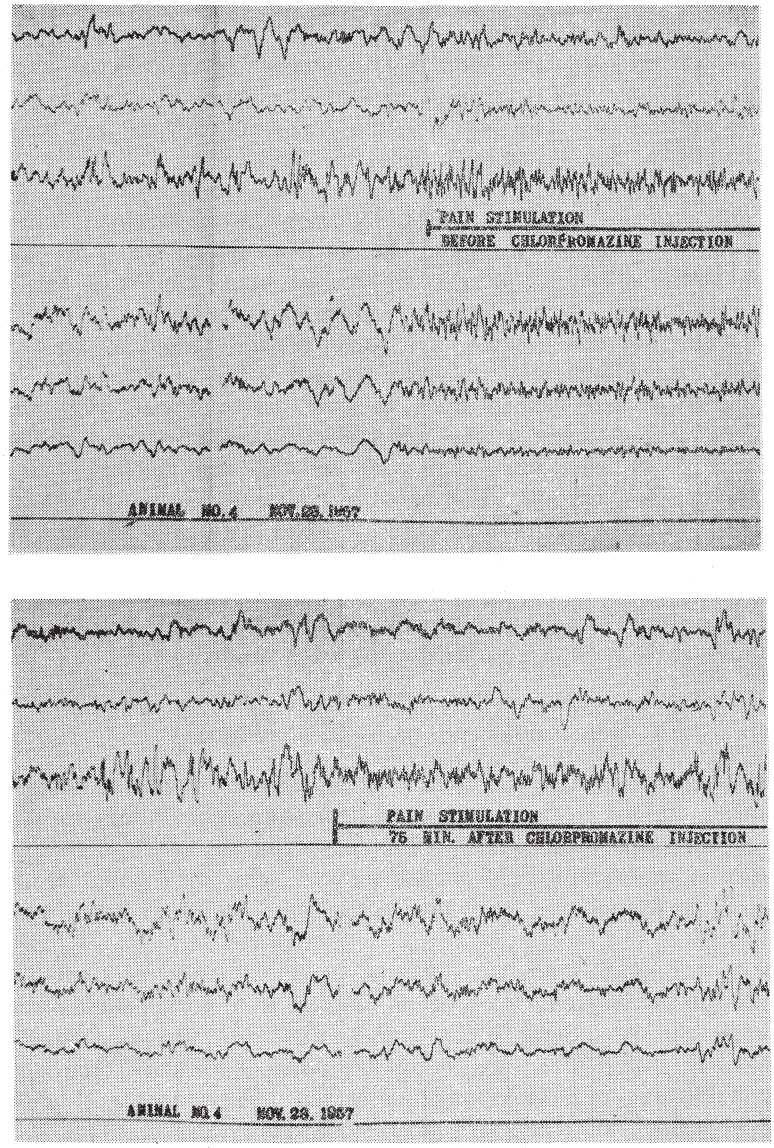

FIG. 13. Affection of chlorpromazine upon the electrocorticogram of adult guinea-pig under the cutaneous pain stimulation. Upper three records are taken from sensory area; lower three from frontal area.

lescribed reactions, were seen in cardiovascular system; the changes of the blood ›ressure and pulse rate. Blood pressure rose immediately after the muscle vork and at this time the systolic pressure was the maximum, then it lowered 'elatively rapidly and recovered to nearly initial resting pressure within 10 or .5 minutes. The same was with the pulse rate.

The systolic pressure rose about 10–20%, the diastolic pressure lowered about 20%, and pulse rate elevated about 20–30% in normal healthy subjects.

These somatic changes associated with muscle exercise are the consequence of the vital reactions, the mechanism of which is too complicated to analyze the implicating factors. The sympathico-adrenomedullary system seems to be an important factor concerned with these vital reactions.

Another important reaction was the cutaneous vasocontraction. This phenomenon was observed not only in the countenance of examined subjects, but also more distinctly in the ear-lobule vessels from which the blood was taken to analyze the blood sugar and cellular components. During a few minutes after the muscle work, it was harder to pipette the peripheral arteriolar blood than during anytime else because of vasocontraction caused by the excitement of sympathico-adrenomedullary system. After this period, the opposing reactions followed; face flashed and it became easy to pipette. These reactions are the rebound phenomena or the postagressive oscillating phenomena.

All these phenomena were depressed by the administration of various sympathicolytics, for example, the blood pressure elevation was lessened to below about 20% three out of four cases. Pulse rate was contrariwise augmented in chlorpromazine-treated cases (Nos. 86 and 87).

Patients with autonomic disorder were also examined, the blood pressure and pulse rate were, however, relatively normoactive than blood sugar level and no significantly pathological evidences were observed.

DISCUSSIONS AND GENERAL CONCLUSIONS

The vital responses may be controlled under the integrated neurohumoral regulationship, among which the sympathico-adrenomedullary system may implicate as an important factor. The participation of this system in the muscle work is experimented in normal subject with or without pretreatment of various sympathicolytics and in the patients suffering from any neurohumoral disorder.

In the preceding chapter, the affection of muscle exercise upon the blood sugar level, the urinary excretion of adrenaline and noradrenalin, the serum lactate level, the peripheral blood cell counts, and somatic manifestations and the afferent action of adrenaline on the cortical evoked potential of pain and other cutaneous stimulation are described independently of each other, and some additional comments are provided in every section.

An increase in adrenomedullary secretion during muscle exercise has been suggested by many investigators in the past (Hartman, Waite and McCordock, 1922[56]; Cannon *et al.*, 1924,[17)18)] 1927,[16)] 1937[15)]; Wada, Seo and Abe, 1935[95)]; von Euler and Hellner, 1952[44)]; Kärki, 1956[65)]; and Elmadjian, 1956,[41)] 1958[39)]), and the direct evidence on the change of suprarenal medulla produced by diverse nocuous agents was reported by Selye (1936)[86] who found that the chromaffinity of the medullary cells were reduced following muscle work and by Hökfelt (1951)[62)] who found a tendency of the adrenaline content of the medulla in the rat to decrease after work.

In my own experiments, the excess output of both adrenaline and noradrenaline was also recognized in the first one hour urine after muscle exercise on bicycle ergometer for five minutes, which was diminished or suppressed markably with the preliminary treatment of various sympathicolytic agents ch as benzyl-imidazoline, phentolamine or chlorpromazine. The intention employ not sole sympathicolytic agent but some kinds is to eliminate the culiar action of one drug and to obtain the results induced by the common mpathicolytic action.

The pharmacological nature of the adrenergic blockade of these sympaicolytics is not yet ascertained. Benfey *et al.* (1958)[10] reported that after radrenaline injection following previous adrenergic blockade there was a riking increased noradrenaline excretion in urine, and postulated that these ugs acted to accelerate the excretion into urine. In our laboratory, enzymatic eakdown of adrenaline was measured manometrically from the point of lrenaline oxidation. So long as to measure the adrenaline oxidation as oxygen take benzyl-imidazoline and chlorpromazine increased the oxygen uptake in ysiological concentration but isoamytal sodium had no effect upon it.[61] From ese results the sympathicolytics adopted here may promote the adrenaline eakdown (probably due to increased enzymatic activity of monoamine oxidase) from Benfey's[10] experimental results catecholamines may be more excreted to urine through inactivation by these drugs.

The reactions following muscle exercise in a specific subjects are illustrated Fig. 14 and 15, in which the results without pretreatment is graphed as lid line and the results with previous treatment of sympathicolytics as dotted ne. Case No. 80 (non pretreatment) is characterized as follows: the urinary cretion of adrenaline and noradrenaline is elevated after muscle exercise and covers to the initial resting level in the next one hour urine, and lactate vel is elevated just after the muscle work which recovers within 15 minutes, e blood sugar level is relatively stable and referable to "stable type", and rmal eosinopenic response one hour after the exercise and moderate leukotosis are observed. In the same subject, these responses are significantly tered by previous injection of chlorpromazine (Case No. 86), that is, the inary excess output of two catecholamines following the muscle exercise isappeares completely, the lactate level rises remarkably and its recovery prolonged, the normal blood sugar pattern "stable type" is replaced by athological pattern "labile type", the one hour eosinopenic response is suppressed and three hour response is diminished, and muscle fatigue is noticeable. he same is in Cases 81 and 83, the former being without preliminary treatent, the latter previously treated with benzyl-imidazoline (Fig. 15). The lood sugar curve is altered from "standard type" to "labile type", associated ith disappearance of excess urinary excretion of adrenaline and noradrenaline.

It has been pointed out that the sympathico-adrenomedullary function is great concernment to regulate the blood sugar level, for example, Cannon 1939)[15] established this fact by determining the effect of emotional excitement n blood sugar before and after sympathetic extirpation and also observed at the denervation of the adrenal glands rendered the animal much more

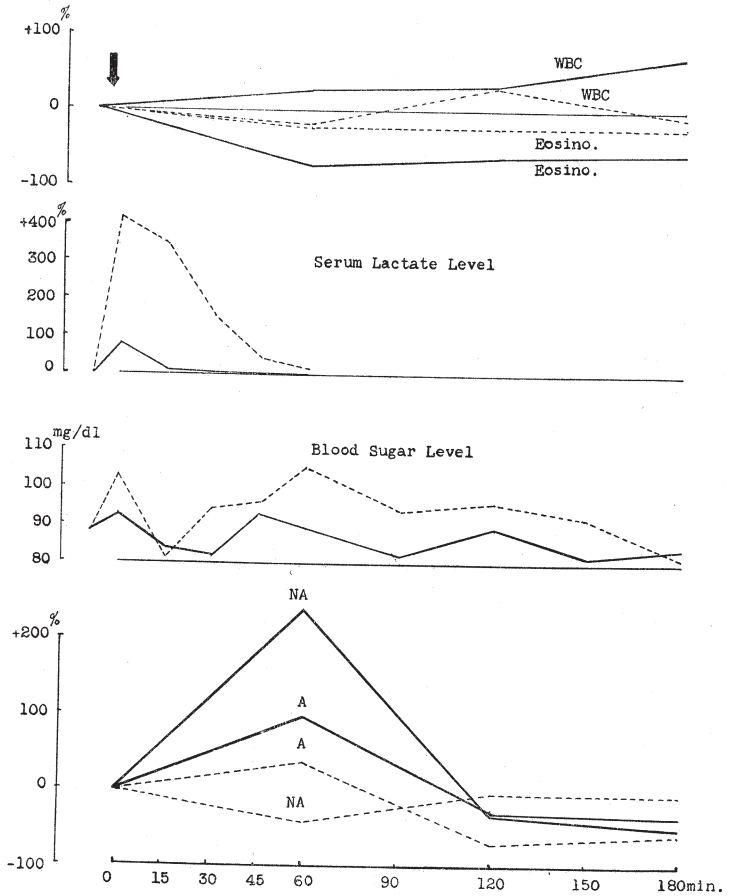

FIG. 14. Effects of sympathicolytic drug (Chlorpromazine injection) upon WBC and eosinophils counts, serum lactate level, blood sugar level, and urinary excretion of adrenaline and noradrenaline following muscle exercise on bicycle ergometer in the same subject.

—— Non-pretreatment (Case No. 80)

---- Chlorpromazine, intramuscularly injected 15 min. prior to muscle exercise (Case No. 86)

sensitive to insulin hypoglycemia.

On the other hand, Gellhorn *et al.* (1941)[40)51)] investigated the carbohydrate metabolism under neurohumoral regulation, from which the vago-insulin system and sympathico-adrenomedullary system were hypothetized as functional units and they concluded that both systems were activated under normal physiologic condition, but the latter ordinarily predominated over the former. This opinion was based on the following experimental data: diverse nocuous stimulations caused hyperglycemia in normal animals, whereas hypoglycemia occurred as

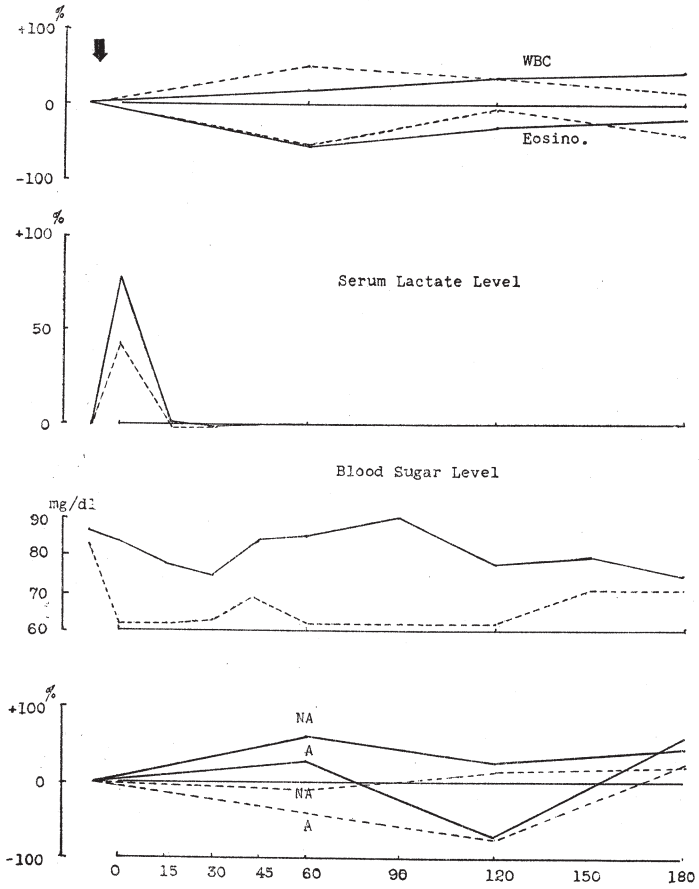

FIG. 15. Effects of sympathicolytic drug (Benzyl-imidazoline injection) upon WBC and eosinophils counts, serum lactate level, blood sugar level, and urinary excretion of adrenaline and noradrenaline following muscle exercise on bicycle ergometer in the same subject.

—— Non pretreatment (Case No. 81)

---- Benzyl-imidazoline, intramuscularly injected 15 min. prior to muscle exercise (Case No. 83)

a consequence of these stresses in adrenodemedullated or adrenalectomized animals.

It is possible to draw the importance of the sympathico-adrenomedullary system in blood sugar homeostasis from these investigations above cited or my own experimental results. However the biochemical, physiological and biologic interpretations are not satisfactory, because the blood sugar level falls not always in the subjects previously treated with sympathicolytics, but also in the subjects whose urinary excess adrenaline excretion disappeared completely.

It is already mentioned that the maintenance of normal levels of blood sugar is one of the most finely regulated of all the homeostatic mechanisms and is influenced by many hormones, autonomic or central nervous system. It needs hardly be mentioned that insulin is one of the decreasing controllers of blood sugar level, however, some kinds of hormones capable to elevate the blood sugar level have been introduced, *i.e.* anterior pituitary hormones, adrenal cortical hormones, glucagon and thyroid hormone, including adrenaline and noradrenaline. These hormones have the same action to elevate the blood sugar, but their natures differ in many respects. The hypoglycemia may be more insidious to the vital livings than hyperglycemia, and thus in order to prevent the vital being from hypoglycemia the regulatory mechanism should be multiple. Accordingly the sympathicolytic injection or administration of the physiological doses, though able to alter the normal responses, is unable to permit the complete disturbance in the homeostasis of blood sugar level. So, provided that adrenaline secretion is diminished or its inactivation is promoted by previous treatment with sympathicolytic agent, the other regulators should collaborate to prevent the resultant hypoglycemia incident to muscle exercise.

The existence of a central neurogenic mechanism for the regulation of carbohydrate metabolism was first recognized by Claude Bernard in 1858 when he observed that piqûre of the fourth ventricle caused glycosuria ("piqûre diabetes"). Within recent decades, it has been established that the hypothalamo-hypophysial neuroendocrine axis is intimately concerned with the regulation and control of carbohydrate metabolism. Lesions in the hypothalamus, particularly in the area of the paraventricular and ventricular nuclei, cause various disturbances of carbohydrate metabolism, *i.e.* hypo- or hyper-glycemia, hyper- or in-sensitivity to insulin, renal glycosuria and so on.[7) 59) 67) 74) 81)]

The control of ACTH secretion by the anterior pituitary gland is attributed to the action of chemical mediators in the brain which arise from the anterior portion of the hypothalamus (Harris, 1951).[55)] These substances reach the pituitary by way of blood vessels which traverse the pituitary stalk; in the gland they excite the basophilic cells to secrete ACTH. The hypothalamic centers themselves are activated through the cerebral cortex by nonspecific stresses, such as cold or psychic reactions. Adrenaline may also stimulate the hypothalamic centers. (Vogt, 1944).[94)] Schayer (1951)[84)] concluded that C^{14}-labelled adrenaline failed to pass the blood-brain-barrier at all; however, such a conclusion is unjustified because there are regional differences in the blood-brain-barrier to adrenaline, so that measurable amounts may enter the hypothalamus.[80)]

The afferent action of adrenaline is examined in my own experiments employing the electrocorticographic studies on adult guinea-pig. These results indicate the definite afferent effect of adrenaline and that this hormone is secreted accompanying with various stimulation, penetrates partially the blood-brain-barrier, enters into cerabral parenchym such as hypothalamus and causes the following multiple efferent actions from there.

In recent years, it has been gradually clarified that adrenaline-hyperglycemia is in part as a consequence of depressed glucose assimilation or utilization by

peripheral tissues (Somogyi, 1950).[87] After muscle exercise, it needs that glucose assimilation from blood stream into muscle is accelerated and muscle synthesize glycogen in itself. Ellis and Anderson (1954)[37] and Walaas and Walaas (1950)[97] postulated the depression of glucose assimilation by adrenaline in skeletal muscle. The regulator of vital reaction activated in muscle exercise is not only the sympathico-adrenomedullary system, but also other multiple systems, for example vago-insulin system as demonstrated by Gellhorn (1941).[49][50] In order to assimilate the glucose into muscle and other tissues, these multiple regulating systems should collaborate, among which vago-insulin system is apparently the most important. Provided that these systems and their regulating center such as hypothalamus are in order, proportionable glucose mobilization from the liver, sufficient glucose assimilation into fatigued muscles and to keep the blood sugar level stable are possible.

Consequently the appreciation of blood sugar process following muscle exercise is available to estimate as to whether the homeostasis in the examined subject is favorable or not.

The effects of the sympathico-adrenomedullary system upon muscle exercise has been investigated for many years, and it was at the end of last century that Orbeli found a phenomenon where stimulation of the sympathetic fibers will increase the contractile tension of the fatigued frog muscle. This classical finding is known as Orbeli's effect. Since then the relationship of the sympathico-adrenomedullary system with muscle contractibility has been investigated. Hartman, Waite and Powell (1922)[57] observed that normal cats showed dilatation of the denervated pupil accompanying work in a treadmill and concluded that such dilatation was probably caused by adrenaline and indicated that adrenaline played a very important role in increasing muscular work and delaying the onset of fatigue. Burn (1945)[14] and Goffart (1952)[51] reported that adrenaline could produce an increase in the contractile force in mammalian skeletal muscle. Clinically muscle fatigue is liable to be lessened by administration of adrenaline. In my own experiment, the subjects who have been injected or administrated perorally with various sympathicolytic agents are remarkably fatigued with the accompaning loss of usual excess urinary excretion of adrenaline and noradrenaline. The excess output of urinary adrenaline is influenced by the intensity and duration of the exercise. After the exercise ceases the increased output of adrenaline persists usually for a few minutes (Hartman, Waite and McCordock, 1922).[56] In my own experiments, the duration of hyperlacticacidemia is within the first one hour and the increased excretion of adrenaline is also in the first one hour urine. The increased production of serum lactate is a consequence of accelerated muscle glycolysis, with which adrenaline is related. As shown in Fig. 1, adrenaline reacts along with tissue components to accelerate the formation of cyclic adenine nucleotide,[74][89] which in turn accelerates the formation of active phosphorylase and that finally alters the steady state of the UDP-glucose[66] and phosphorylase systems[88] in favor of glycogenolysis. The energy storing system consisting of creatine and phosphocreatine depends upon the energy producing system, that is, glycogenolysis in muscle. And thus the contractile myoprotein,

actomyosin, is able to contract without fatigue, provided that these two energy storing and producing systems take a favorable turn when necessary.

Adrenaline is one of the important modulators of muscle contraction to take a favorable turn directly in the energy-producing system, and indirectly in the contraction system.

SUMMARY

1. In order to inquire into the physiological role of the sympathico-adrenomedullary system under the vital reactions, the chemical and cellular contents in blood and urine were measured.

2. The affection of muscle work on a bicycle ergometer upon the blood sugar level, the serum lactate level, the peripheral white blood cell and eosinophil counts, and urinary excretion of adrenaline and noradrenaline were determined in normal human subjects with or without pretreatment of sympathicolytic agents and in the patients with some neurohumoral disorder.

3. Following muscle exercise, hyperlacticacidemia, leukocytosis, eosinopenia (even one hour after the exercise), increased uninary excretion of adrenaline and noradrenaline were observed, all of which were altered by the previous sympathicolytic treatment or in the patients.

4. Muscle exercise activates the sympathico-adrenomedullary system, and promotes the intrinsic adrenaline secretion.

5. Adrenaline thus secreted has the relationship with muscle glycogenolysis, probably through the activation of muscle phosphorylase, to smooth the muscle work and prevent from over-fatigue.

6. Blood sugar pattern after muscle work is usually stable or regularly fluctuated in normal subjects, but it is replaced by labile or irregularily fluctuated pattern in the pretreated and pathologic subjects.

7. It is obvious that the homeostasis of blood sugar level after muscle exercise is modulated positively by the sympathico-adrenomedullary system, however it is not the sole regulator to mobilize the sugar.

8. Adrenline has not only the strong metabolic effect but also the definite affectiveness to the central nervous system.

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