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*From the Third Medical Clinic, Kyoto University Hospital
(Director: Professor M. Maekawa, M. D.)*

**Experimental Chronic Neurogenic Hypertension in Dogs with
Piarachnitis Adhesiva Thoracolumbalis Spinalis (I)
Chronic Effect of Alumina-Cream-Induced Piarachnitis
Adhesiva upon the Arterial Blood Pressure**

By

AKINA HIRAKAWA

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The importance of arteriolar vasospasm in essential hypertension has been emphasized by Guyton¹⁾ as follows: "Any theory that attempts to explain the mechanism of essential hypertension must also explain the intense arteriolar constriction that causes the increased peripheral resistance in this disease".

Indeed the question of the arteriolar vasospasm constitutes the crucial point in any hypothesis dealing with the pathogenesis of essential hypertension.

Since the turn of this century, extensive researches on the pathogenesis of essential hypertension have been carried out, which culminated in the formation of four main concepts, based mainly on experimental hypertension, namely, the neurogenic, renal, endocrine and humoral. They are: experimental hypertension due to the removal of moderator nerves by Hering²⁾, the experimental renal hypertension by Goldblatt³⁾ and subsequently by Page⁴⁾, Grollman⁵⁾, Dick⁶⁾, the experimental DCA hypertension by Selye⁷⁾, and the experimental renoprival hypertension by Grollman⁸⁾.

Various hypotheses on the pathogenesis of essential hypertension, based on knowledges of these experimental hypertension, all explained the arteriolar vasospasm but often failed to explain what clinicians encounter at bedside in the patients with essential hypertension. Real pathogenesis of essential hypertension still remains in ambiguity

at the present moment, a situation calling for further studies of clinical "facts" and for accumulation of more and more experimental works or new working hypotheses.

Maekawa⁹⁾ has formulated a theory that the arteriolar vasospasm in any type of hypertension depended on disturbances in APT-ATPase system of the general vascular system including the kidneys, and a number of clinical and experimental evidences have accumulated in support of this theory. Motomura¹⁰⁾ noted increased ATPase activity in the serum of patients with essential hypertension as compared with normal controls. Nakajima¹¹⁾ demonstrated that a dog-kidney-extract with high ATPase activity was a strong pressor substance. Matsunaga¹²⁾ isolated from the serum of essential hypertensive patients a fraction with ATPase activity which was also a strong pressor substance.

Moreover, Maekawa¹³⁾ postulated that aforementioned disturbances in ATP-ATPase system of the blood vessels in human essential hypertension were ascribable to the functional derangement in the kidneys, and this derangement was probably due to the renal ischemia which occurred as a result of increased tonic sympathetic supply to the renal blood vessels owing to chronic stimulation of the renal vasomotor center in the spinal cord, when it was involved in subclinical adhesive arachnoiditis.

The present work to be described in this

Fig. 1. Variation in the blood pressure following the treatment with the alumina cream. Five figures from above represent 5 laminectomized-injected dogs, while the 2 figures at the bottom represent 2 non-laminectomized-injected dogs. The shaded parts in each figure represent the increase above the initial level with reference to mean blood pressure.

paper has been undertaken to produce in dog an experimental counterpart of such hypothetical processes of hypertension, adhesive arachnoiditis being produced by intrathecally injected alumina cream.

METHODS

(1) Animals

Seven mongrel dogs have been used. Those dogs with pre-existing hypertension or abnormal electrocardiograms and those restless during blood pressure recordings have been excluded from the series.

(2) Blood Pressure Measurements

Dogs, unanesthetized, were fixed on a table in supine position and blood pressures were recorded from a femoral artery by an electromanometer, systolic, diastolic and mean blood pressure being recorded oscillographically. The needle used for puncture measured 0.7 mm. in diameter internally, and physiological saline solution with heparin was used for preventing the blood from clotting inside the recording system. Pressures were taken after the dog has been fixed to the table and lain quiet for more than 5 minutes.

(3) Alumina Cream

One % alum ammoniacal water was added to 1 % ammonium water and the resulting precipitate was washed thoroughly with centrifugation (3000 RPM for 5 minutes) with aseptic distilled water^{14) 15)}. This final precipitate was used each time after diluting it with two to ten volumes of physiological saline solution.

(4) Intrathecal Injection of Alumina Cream

After several blood pressure takings have been made in dogs, they were subjected to intrathecal injection of alumina cream fluid under intraperitoneal anesthesia with sodium amobarbital in doses of 50 mg. per kg. body weight, after laminectomy.

After laminectomy, 5 dogs were injected with alumina cream in different concentrations and at varying doses as follows: 1:2 dilution in 0.7 ml. (1 dog), 1:2 dilution in 0.5 ml. (2 dogs), 1:10 dilution in 0.2 ml. (2 dogs). At the level of 1st lumbar vertebra, a fine, bent needle was inserted, through a small incision previously made through the dura mater, craniowards beneath the meninges and the fluid was injected at a slow rate.

In the remaining two dogs, which served as controls, no laminectomy has been performed. In these dogs a 1:10 dilution fluid in dose of 1.5 ml.,

TABLE I RESPONSE OF MEAN ARTERIAL BLOOD PRESSURE IN mmHg
(*Bold Type: Increase above 15mmHg*)

		Control Animals. (Paravertebral Injection)		Experimental Animals. (Intrathecal Injection)				
No. of Dogs		457	459	461	467	454	451	462
Alumina Cream	Dilution Volume	1:10 1.5ml.	1:10 1.0ml.	1:2 0.7ml.	1:2 0.5ml.	1:2 0.5ml.	1:10 0.2ml.	1:10 0.2ml.
Initial Blood Pressure		115	134	128	106	131	107	145
Blood Pressure Responses								
1. week								
2.		0	-31		+22			
3.				+24				-26
4.		-2		+25				
5.			-24		+27	-29		
6.								+16
7.		+1			+28	+19	+6	+7
8.			+4	+34			+16	-6
9.			-13		+18			
10.				+22		+41		
11.		-14			+5	+5	+23	
12.				+27			+18	+6
13.			+10	+26				+22
14.								
15.		+9	+4	+9		-3		+11
16.					-6			
17.		+18	+3				+25	
18.							+43	-24
19.		+8	-3	+7				
20.		+24					+3	-6
21.		+20	-19					
22.								
23.								
24.		+5						
25.			-3					
26.								
27.								
28.		+10						

and 1.0 ml., respectively, was injected by way of intervertebral foramina towards the spinal cords along the nerve sheaths.

(5) Post-operative Observations

Both operated dogs and controls have been reexamined at various intervals for blood pressure, electrocardiogram, urine and general conditions for the period of one to one and a half year, whereupon they were sacrificed and various organs were studied for histological alterations with hematoxylin-eosine staining.

RESULTS

(1) General Conditions

Following the operation, some of dogs exhibited temporarily slight motor disturbances of the hind limbs, which, however, regressed soon.

At the end of three post-operative months, some of the dogs, well-tempered previously, became somewhat rough and excitable, but this changes also soon subsided, and no dogs showed convulsive fits. There were no changes in appetite and other general conditions of the dogs, and all

the dogs remained apparently quite healthy till the time of sacrifice, except for one dog which was lost during the observation period.

(2) Electrocardiogram

Electrocardiograms recorded between the 3rd and 6th post-operative month were not changed significantly from those recorded prior to the operation.

(3) Urine

Slight albuminuria occasionally appeared following the operation, which, however, subsided after a short period of time. Urine remained essentially unchanged before and after the operation and no instance of hematuria was noted.

(4) Mean Blood Pressure

Changes in the mean blood pressure following the operation are listed in Fig. 1. and TABLE I. Inspection of these table and figure indicated that the injection of alumina cream fluid in 1:2 dilution and in doses over 0.5 ml. subarachnoideally at the level of the 1st lumbar vertebra in 3 dogs (No. 461, No. 467, No. 454) was followed by a

TABLE II RESPONSE OF SYSTOLIC ARTERIAL BLOOD PRESSURE IN mmHg
(*Bold Type: Increase above 15mmHg*)

		Control Animals. (Paravertebral Injection)		Experimental Animals. (Intrathecal Injection)				
No. of Dogs		457	459	461	467	454	451	462
Alumina Cream	Dilution Volume	1:10 1.5ml.	1:10 1.0ml.	1:2 0.7ml.	1:2 0.5ml.	1:2 0.5ml.	1:10 0.2ml.	1:10 0.2ml.
Initial Blood Pressure		202	195	202	154	207	155	250
Blood Pressure Responses								
1. week					+52			
2.		- 2	-49					
3.				+25			-27	
4.		- 8		+36				
5.			-39		+73	-28		
6.								+23
7.		-17			+51	+31	+ 3	-13
8.			+ 7	+32			+ 8	-19
9.			-16		+34			
10.				+36		+38		
11.		- 3			+32	+40	+24	
12.				+ 5				-10
13.							+29	
14.			+32	+39				+24
15.								
16.		+37	+15	+36		+12		+ 9
17.					+ 4			
18.		+39	+10				+16	
19.							+40	-76
20.		+31	+11	+ 3			- 6	-14
21.		+36						
22.		+50	- 9					
23.								
24.		+52						
25.			+ 5					
26.								
27.								
28.		+23						

rise in the blood pressure beginning in the first (No. 467), the third (No. 461), or the 7th (No. 454) post-operative week.

The peak of the rise was attained between the 5th and 10th week. The magnitude of the rise ranged between 28 and 41 mm.Hg. Between the 11th and 16th week the blood pressure returned nearly to pre-operative levels. With alumina cream fluid at 1:10 dilution and in as small a dose as 0.2 ml. (No. 451, No. 462), the blood pressure still rose between the 6th and 7th post-operative week, the peak being reached between the 11th and 15th week. The magnitude of the rise was 22 to 23 mm.Hg, the blood pressure returning to previous levels between the 19th and 21st week. It will be noted that blood pressure changes in the latter group were later in onset and smaller in magnitude in comparison with blood pressure changes in the former group.

The control dogs, injected with alumina cream fluid at 1:10 dilution and dose of 1.0 to 1.5 ml. by the route of intervertebral foramina along the

nerve sheaths (No. 457, No. 459), showed insignificant rise in blood pressure during 17 weeks after operation, the rise being smaller than 10 mm.Hg. Blood pressure showed fluctuation around the base line of the pre-operative level and apparent rise in blood pressure occurred only during the winter season in one dog (No. 457), when the pressure rose by 24 mm.Hg but for a transient period of time.

(5) Systolic Blood Pressure

Changes in the systolic blood pressure following the operation are tabulated in TABLE II and illustrated in Fig. 1.

The 3 dogs (No. 461, No. 467, No. 454) injected with 0.5 ml. or more of 1:2 dilution fluid of alumina cream at the level of the 1st lumbar vertebra showed elevation in blood pressures, beginning in the 1st (No. 467), the 3rd (No. 461), or the 7th (No. 454) week, the peak of the rise being attained between the 5th and the 11th week. The magnitude of the observed rise ranged between 36 and 73 mm.Hg. The pressure return-

TABLE III RESPONSE OF DIASTOLIC ARTERIAL BLOOD PRESSURE IN mmHg
(*Bold Type: Increase above 15mmHg*)

		Control Animals. (Paravertebral Injection)		Experimental Animals. (Intrathecal Injection)				
No. of Dogs		457	459	461	467	454	451	462
Alumina Cream	Dilution Volume	1:10 1.5ml.	1:10 1.0ml.	1:2 0.7ml.	1:2 0.5ml.	1:2 0.5ml.	1:10 0.2ml.	1:10 0.2ml.
Initial Blood Pressure		87	109	109	88	110	75	117
Blood Pressure Responses								
1. week					+20			
2.		+ 1	-29					
3.				+14				
4.		- 1		+ 7			- 9	
5.			-17		+23	-12		
6.								+25
7.		0			+22	+ 6	+ 9	+ 5
8.			+ 6	+36			+30	-11
9.			- 6		+ 9			
10.				+15		+32		
11.		-12			- 7	-20	+33	
12.				+ 2				+13
13.							+21	
14.			+ 9	+ 3				+ 9
15.								
16.		+25	+ 7	- 3		- 6		+ 3
17.					-10			
18.		+ 2	+ 9				+26	
19.							+50	-19
20.		- 3	-17	- 2				
21.		+15					+21	-16
22.		- 7	-17					
23.								
24.		0						
25.			- 5					
26.								
27.								
28.		+ 4						

ed nearly to the pre-operative levels between the 16th and 20th week. With 1:10 dilution fluid of alumina cream in as small a dose as 0.2 ml. (No. 451, No. 462), systolic blood pressures still rose between the 6th and 8th week and returned down to the previous level within 16 weeks. In these instances, however, the rise was but 23 to 29 mm.Hg in magnitude and was definitely smaller than the group injected with more concentrated fluids.

The control dogs (No. 457, No. 459) which received injection fluid at 1:10 dilution in dose of 1.0 to 1.5 ml. by the route of intervertebral foramina along the nerve sheaths, maintained their systolic blood pressures, at least during 13 weeks following the operation, not in excess of 7 mm. Hg above the pre-operative levels. After the 14th week, the winter season set in, and the systolic blood pressures rose by 32 to 52 mm.Hg in this group.

(6) Diastolic Blood Pressure

Changes in diastolic blood pressure following the operation are listed in TABLE III and illustrated in Fig. 1. With 1:2 dilution fluid of alumina cream in dose of 0.5 ml. or more, injected at the level of 1st lumbar vertebra (No. 461, No. 467, No. 454), the diastolic

blood pressure began to rise in the 1st (No. 467), the 3rd (No. 461), or the 7th (No. 454) post-operative week, the peak of the rise being attained in 5 to 10 weeks. The magnitude of the rise ranged between 23 to 36 mm.Hg. The pressure returned down closely to the previous level in 11 or 12 weeks.

With as small a dose as 0.2 ml. of 1:10 dilution fluid of alumina cream (No. 451, No. 462), diastolic pressures still rose, beginning at the 6th or 8th week, and the peaks being attained at the 6th or 11th week. The magnitude of the rise ranged between 25 and 33 mm.Hg, and the pressures returned to the pre-operative levels in 16 weeks.

The control dogs, injected with 1:10 dilution fluid in dose of 1.0 to 1.5 ml. by the route of intervertebral foramina along the nerve sheaths, maintained their diastolic blood pressures at least within 13 weeks after the operation not excess of 6 mm.Hg above the pre-operative levels. The winter season setting in after the 14th week, diastolic blood pressure rose by 9 to 25 mm.Hg but for a transient period of time.

(7) Histological Changes

Kidneys——In those dogs which could be made hypertensive (No. 461, No. 454, No. 451,

Fig. 2. No. 461. See the endothelial proliferation in vas afferens glomeruli. Hematoxylin-eosine staining.

No. 462), the characteristic feature of histological changes in kidneys was the proliferation of endothelial cells in vas afferens glomeruli, as shown in Fig. 2. (from No. 461) and Fig. 3. (from No. 461). This kind of proliferation was entirely lacking in the control group, as represented by essentially unchanged kidney of a control dog No. 459 shown in Fig. 4.

Such glomerular alterations as shown in Fig. 2 and 3 were patchy in distribution but occurred fairly constantly in the hypertensive dogs. Besides this, there was degeneration of tubules and of the wall of larger blood vessels as well as thickening of Bowman's capsules, which were unspecific, however, since the same alterations were noted in the control group as well.

Heart — The hypertensive dogs (No. 461, No. 454, No. 451, No. 462) characteristically showed thickening of the wall in small arteries of the heart, such as shown in Fig. 5. which was taken from dog No. 461. This finding was entirely lacking in the control group.

Spinal Cord — In hypertensive group (No.

461, No. 454, No. 451, No. 462), there was a thickening of the meninges, such as shown in Fig. 6., which was taken from the lower thoracic segments of spinal cord in dog No. 461. There was also cavitation in the spinal cord situated in such way that main part of the cavity was seated in the posterior half of the spinal cord, as represented by the specimen given in Fig. 7. which was taken from the lower thoracic segments of dog No. 461. Such cavitations were short in extent in the craniocaudal direction, and occurred nearly at the centre of the portion of the spinal cord showing marked thickening of the meninges.

As inspection of Fig. 8. indicates, which was taken from the lower thoracic segments of dog No. 461, alterations of the meninges consisted of thickening of dura mater and cellular proliferation in the pial space between the pia and arachnoidea, and this area of cellular proliferation occasionally involved vessels.

Alterations such as described above never occurred in the control group (No. 457, No. 459).

Fig. 3. No. 461. See the endothelial proliferation in vas afferens glomeruli. Hematoxylin-eosine staining.

Fig. 4. No. 459, a control dog. The kidneys show normal histology. Hematoxylin-eosine staining.

Fig. 5. No. 461. See the thickening of the wall of a small artery in the heart. Hematoxylin-eosine staining.

Fig. 6. No. 461. The spinal cord at L1-level. There is cellular proliferation and thickening of dura mater. Hematoxylin-eosine staining.

Fig. 7. No. 461. The spinal cord at L1-level. In addition to cellular proliferation and thickening of dura mater, there are cavitation and enlargement of the central canal. This section and the section shown in Fig. 6. were obtained from 2 regions of the spinal cord only 1 cm. apart from each other. Hematoxylin-eosine staining.

Fig. 8. No. 461. The spinal cord at L1-level. There is thickening of dura mater and the piarachnoid adhesion involving blood vessels. Hematoxylin-eosine staining.

DISCUSSION

To recapitulate the points already described, the present experiment has been carried out on a total of 7 dogs, 5 of them being laminectomized and the rest 2 control dogs non-laminectomized.

In the laminectomized group, the dura mater, exposed at the level of 1st lumbar vertebra, received a small incision and small amounts of alumina cream fluid was injected intrathecally craniowards through this incision. Following the operation, the blood pressure definitely rose above the pre-operative level after a certain latent time.

In contrast to this, non-laminectomized group of 2 dogs, which simply received small amounts of alumina cream fluid along the nerve sheaths by the route of intervertebral foramina, did not show any significant rise in blood pressure.

In this part of the paper, some salient points will be discussed with regard to (1) clinical "facts"

in human essential hypertension which formed the starting line for the present experiment, and (2) a hypothesis concerning the possible mechanism involved in the genesis of essential hypertension in man, and (3) the present experiment which has been carried out on animals.

(1) Clinical "Facts" in Essential Hypertension

Subclinical Adhesive Spinal Arachnoiditis

According to Maekawa, Konishi et al¹⁶⁾ who performed detailed myelographical examination of the spinal cord in 48 cases of essential hypertension and compared the results with those obtained from similar examinations in 410 cases of other diseases, pictures of adhesion occurred with higher frequency of incidence in the hypertensive group at the level of the 11th dorsal vertebra posteriorly than in the non-hypertensive group, the difference being statistically significant with $P < 0.001$.

Clinically, the history of the study on arachnoiditis dates back to that of Krause¹⁷⁾, Oppenheim¹⁸⁾, Horley¹⁹⁾ who first described this disorder from surgeon's viewpoint. Subsequent development of myelography and pneumoencephalography made the recognition possible of arachnoiditis spinalis or arachnoiditis cerebri to the internists, and the numerous reports have accumulated on this disease²⁰⁾. However, incidence of spinal arachnoiditis in association with various specific internal diseases has not been studied systematically till today except for a series of statistical investigation on this problem by Maekawa and his students.

Maekawa²¹⁾ already noted significantly frequent association of adhesive spinal arachnoiditis at the high thoracic levels with neurocirculatory asthenia²²⁾ and angina pectoris²³⁾ on the basis of numerous myelographical examinations, which is again a unique approach to the problem as of today. One may question whether a given patch of apparent passage disturbance to the flow of contrast medium in a myelogram should always prove to be a focus of anatomicohistologically substantiable adhesive arachnoiditis. This question remains to be a matter of the future investigation, but a few available cases of autopsy suggested a fairly close correspondence between the radiological and histological findings²⁴⁾.

Degeneration of Lateral Horn Cells——

According to the report of Morimoto²⁵⁾, who examined 3 autopsied cases of essential hypertension for histological alterations in the spinal cord, there was constant finding of degeneration of lateral horn cells involving larger fractions of total observed number of the lateral horn cells than in other diseases. As compared with cancer, myocardial infarction, valvular heart diseases, calculus in urinary tract, chronic nephritis, trauma, cirrhosis of the liver and malnutrition, different were the behaviors of essential hypertension, peptic ulcers²⁶⁾ and bronchial asthma with regard to histological alterations in the lateral horn cells; namely, the latter group of diseases had greater proportion of lateral horn cells degenerated than did the former group.

Cold Pressor Test——According to Natori²⁷⁾, who examined the patients with essential hypertension for their cold pressor responses to the application of cold to the palm and sole and compared relative magnitude of pressor responses

from the two regions, the responses were more intense from the palm than from the sole, and this results was taken to indicate increased tonic sympathetic discharge from the lower thoracic segments in the individuals with essential hypertension.

Petechiodermogram——According to the preliminary observation by Hirakawa²⁸⁾, who examined patients with essential hypertension for areas of apparent capillary fragility aberrancy with the method of petechiometry, suggestive evidence could be obtained indicating that there was increased vasoconstrictive tone in the cutaneous area of the lower thoracic to higher lumbar segments.

The four clinical "facts" concerning human essential hypertension enumerated above seem to be pertinent to such mechanism of the pathogenesis of essential hypertension as proposed by Maekawa¹³⁾, outline in the next chapter.

(2) Probable Mechanism of the Pathogenesis of Essential Hypertension Proposed by Maekawa

The vasomotor fibre to the kidneys leaves the spinal cord through the anterior thoracic roots between the 6th and 13th segment, particularly through the 11th, 12th and 13th anterior roots in dog and course through the splanchnic nerve, according to Bradford²⁹⁾.

In man the kidneys receive sympathetic neurons from the 12th thoracic and 1st lumbar segment³⁰⁾.

It was exactly at this level, namely at the level of the 11th dorsal vertebra housing the 12th thoracic to the 1st lumbar segment of the spinal cord that Maekawa¹⁶⁾ found myelographically frequent incidence of subclinical adhesive arachnoiditis in the patients with essential hypertension with statistical significance when compared with the patients suffering from other diseases. This fact constitutes a suggestive evidence that the pathogenesis of human essential hypertension depends on functional disturbances or excitation in the vasomotor center of the kidneys.

This postulation is supported by several other clinical "facts", such as the observation by Morimoto²⁵⁾ who found extensive involvement of the lateral horn cells in degenerative processes in the autopsied cases of essential hypertension, or the observation with cold pressor test by Natori²⁷⁾

who obtained cold responses in the subject with essential hypertension which were pertinent to the sympathetically hyperactive state of the lower half of the spinal cord, which houses the vasomotor center of the kidney, or the observation by Hirakawa²⁸⁾ who presented suggestive evidences that there was increased vasoconstrictive tone in the subjects with essential hypertension in cutaneous areas of the lower thoracic to higher lumbar segments, a finding which may be taken to indicate increased tonic sympathetic discharge from the region of the spinal cord housing vasomotor center of the kidneys.

According to Maekawa²¹⁾, subclinical adhesive arachnoiditis at specific level of spinal cord plays a key role in the pathogenesis of certain specific diseases. In neurocirculatory asthenia also, where functional disturbances selectively centre around the heart, one must postulate, and correctly as shown elsewhere^{22) 23)}, the existence of specific moment which is capable of summation or diversion of nervous impulses selectively to the heart. Such moment, according to Maekawa, is played in all possibilities by subclinical adhesive arachnoiditis. Being chronic in nature and extramedullary in location, a focus of subclinical adhesive arachnoiditis is capable of producing such local spinal moment which is required for selective occurrence of functional disorders in specific, segmentally innervated organ.

The arachnoiditis-theory of pathogenesis of essential hypertension constitutes but a part of his concepts of subclinical adhesive arachnoiditis in organ-selecting mechanisms in various diseases.

It seems to be a valid theory that the essential hypertension is initiated by functional derangements in the kidneys as the results of the exposure of renal vascular beds to excessive impulses from the renal vasomotor center, which through involvement in the subclinical adhesive arachnoiditis possibly produces the local moment of summation or deviation of nervous impulses to the kidneys.

If it is hypothetically assumed, and rightly so as supported by indirect clinical evidences, that renal vasomotor center in the spinal cord is in a state of increased activity, particularly with regard to tonic sympathetic activity, it may become easy to understand why renal ischemia should occur in neurogenic initiation of the es-

sential hypertension.

To verify this hypothesis in experimental animals was the purpose of the present investigation, in which adhesive arachnoiditis was artificially induced in dog selectively around the portion of the spinal cord housing the vasomotor center for the kidneys, by injecting small amounts of alumina cream fluid, a chemical substance capable of inducing epilepsy if it were applied to the cerebral cortex, their blood pressure being measured at frequent intervals to determine if there occurs any elevation in the blood pressure.

(3) Discussion of the Results

Extramedullary and Intramedullary Changes Produced—In the present experiment in which alumina cream fluid was injected intrathecally at the level of the 1st lumbar vertebra, resultant changes in the meninges were found also localized at this level.

The most conspicuous of the changes thus produced was the formation of adhesive arachnoiditis, which consisted of thickening of the dura and cellular proliferation within piaarachnoid space, limited in extent within 1 to 2 centimeters centering around the 1st lumbar vertebra.

The hitherto described experimental spinal arachnoiditis produced by injection of foreign bodies like talc^{31) 32) 33)}, kaolin³⁴⁾ and pantopaque³⁴⁾ or, more recently, detergents³⁵⁾, depended on the method of cisternal injection and it was inevitable under such conditions for the animals to become moribund after short period of time, or else animals of longer survivals showed no marked picture of arachnoiditis. Also, in such experiments the arachnoiditis was localized spinally to the cervical segments. To the author's knowledge Ono was the first to describe the type of experiment in which adhesive arachnoiditis was produced artificially in a limited portion of the spinal cord with the aid of alumina cream.³⁶⁾

Experimental production of similar adhesive arachnoiditis localized to the lower thoracic or upper lumbar cord segments, in animals of one year or longer period of survival, as described in this paper, has never been described previously.

The author's results coincided with previous ones with regard to histological changes in that there were thickening of dura mater and cellular proliferation within the piaarachnoid space.

Of intramedullary changes produced, the most conspicuous were the cavitation and enlargement of central canal. Ingraham³⁴⁾ has already described the cavitation associating experimental adhesive arachnoiditis in dogs, which he ascribed to the disturbance of blood circulation within the spinal cord, an apparently valid explanation of the finding. It must be noted that the cavitation in the author's series was markedly limited in extent in the sense that it occupied only small area nearly at the centre of the region of spinal cord involved in the thickening of the meninges.

Blood Pressure Responses—— The blood pressure of dogs seems to be subject to seasonal variation, being higher in cold winter season and lower in hot summer season. To avoid this effect of seasonal variations, the experiment was commenced in the summer season where dog's blood pressure was generally low.

Owing to the chronic nature of the experiment, the winter set in during the course of the experiment, and one of the control dogs began to give high blood pressure readings.

However, this seasonal factor did not materially interfere with the comparison of blood pressure responses in the two groups of animals, because the laminectomized group of dogs, during the summer season, showed much greater elevation in blood pressure than the control dogs for the period of 13 to 16 weeks.

Since the author was under the impression that white dogs were more resistant to blood pressure elevation than black dogs, no white dog was used in the present experiment.

With regard to the relation of the amount and concentration of the injection-material to the resulting pressor response, inspection of TABLE I to III allows following statement: the group of two dogs (No. 451, No. 462) injected with more dilute material in smaller doses was slower in responding with elevation in blood pressure and more labile in maintenance of the elevated blood pressure than the group of 3 dogs (No. 461, No. 467, No. 454) injected with more concentrated material and in larger doses. It appears that an adequate amount of properly concentrated alumina cream fluid must be injected to produce a significant and durable rise in the blood pressure.

Whether there is a parallelism between the severity of inflammatory responses in the

piarachnoid space and the degree of blood pressure elevation, is a question which can not be answered immediately from this experiments, because there is such a great time lag between the blood pressure determinations and the histological examination of the piarachnoiditis that the function and the histology can hardly be compared on the same plane. That the presence of alumina-cream-induced adhesive arachnoiditis was the essential factor in the production of blood pressure elevation appears to be beyond doubt, in view of the fact that the hypertensive dogs were invariably associated with adhesive arachnoiditis or cavitation of the type shown in figure 6 and 7, while the control dogs which remained normotensive were free of such histological alterations.

Whether the observed elevation in the blood pressure was due to local pharmacological action of alumina cream or due to neuro-physiological influence of local adhesive arachnoiditis remains to be decided.

The available literature fails to shed light on this problem, because unfortunately, the length of time required for the establishment of an experimentally produced arachnoiditis³¹⁾ happens to coincide with that required before the first attack of epilepsy is called forth by the experimental application of alumina cream^{14) 15)}, the former being 19 days and the latter being 20 days approximately.

One may question if experimental hypertension similar to the presently described one may not be produced when portions of the spinal cord other than the lower thoracic or the upper lumbar segments are subjected to artificial manipulation, a crucial point which must be tested in later investigations.

(4) Consideration of the Probable Mechanism

The present experiment, intended to testify the validity of Maekawa's theory on the probable mechanism in the genesis of essential hypertension, seems to have significantly substantiated certain aspect of this theory. According to this theory, apparent functional derangement in the kidneys depends on the involvement of the spinal renal vasomotor center in the process of subclinical spinal adhesive arachnoiditis, which produce a local momentum to increase tonic sympathetic

discharges to the kidneys, possibly through the mechanism of summation and deviation of efferent impulses, with consequent renal ischemia which contributes to the initiation of the essential hypertension. This theory has been considerably substantiated by the present animal experiment in which artificial involvement of the renal vasomotor center areas of the spinal cord in the alumina-cream-induced experimental adhesive arachnoiditis gave rise to a hypertension of 13 to 16 week duration and 22 mm.Hg or more above the base line both in systolic and diastolic blood pressure.

Evidently much remains to be elucidated before the pathogenesis of the presently described experimental hypertension is claimed to be understood, just as much difficulty exists in the explanation of pathogenesis in human essential hypertension. To approach the problem of pathogenesis, variations in the cardiac output, renal blood flow, systemic peripheral resistance and blood levels of circulating pressor substances must be determined as well as relative effect of different methods of spinal cord intervention must be assessed.

Various methods have been described to produce experimental hypertension neurogenically, including classical work of Hering's moderator nerver removal²⁾, the experiment of psychogenic stimulation type³⁷⁾, brain lesion^{38) 39) 40) 41)} and electrical stimulation of the splanchnic nerve and others^{42) 43)}, and they considerably widened our knowledge concerning the pathogenesis of essential hypertension.

While these investigations on experimental neurogenic hypertension were important in pointing out three main factors responsible for neurogenic initiation of hypertension, psychogenic, cerebral and peripheral nerve factors, the pathway required for the renal mediation of the neurogenic hypertension has remained un-approached until the present investigation of the author's in which the spinal cord factor was emphasized as an important participant in the genesis of the neurogenic hypertension with renal mediation.

If the presently described experimental hypertension is a reality, which apparently bespeaks for the mechanism of spinally conditioned renal mediation in the neurogenic hypertension, it then must be taken to voice the need of

rerecognition of the spinal control of renal functions and contribute to the elucidation of possible role played by the spinal factor also in the genesis of essential hypertension.

SUMMARY

(1) Five dogs have been injected intrathecally with small amounts of alumina cream fluid after laminectomy at the level of 1st lumbar vertebra.

It was thus possible, without directly manipulating the kidneys, to produce an elevation in the blood pressure for the period of 13 to 16 weeks after the operation by 22 mm.Hg or more above the pre-operative blood pressure level both in systolic and diastolic blood pressure (Fig. 1. TABLE I, II, III).

(2) Nearly all the dogs survived one year or more in good conditions, whereupon they were sacrificed for histological examinations.

Adhesive arachnoiditis localized to the lower thoracic to upper lumbar segments (Fig. 6 and 7), the proliferation of vas afferens glomeruli (Fig. 2 and 3) and the thickening of the wall of blood vessels in the heart (Fig. 5) were noted.

(3) Control experiment has been carried out on 2 dogs, in which small amounts of alumina cream fluid were injected, not with laminectomy, but by the route of intervertebral foramina along the nerve sheaths. There was neither rise in the blood pressure (Fig. 1, TABLE I, II, III) nor histological changes in the meninges or kidneys (Fig. 4).

(4) The results of this experiment seem to substantiate Maekawa's theory concerning the probable mechanism in the pathogenesis of essential hypertension that the possible derangement in renal functions in this diseases is due to the presence of subclinical spinal adhesive arachnoiditis at the level of renal vasomotor centre.

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