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University of Louisville

STUDIES ON SPINAL ANESTHESIA

A Dissertation

Submitted to the Faculty

of the

Graduate School of the University of Louisville

In Partial Fulfillment of the

Requirements for the Degree

of

Master of Science

Department of Pharmacology

By

Frederic E. Shaffer

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Date June 14, 1945

Approved by

Committee:

A. J. Miller

P. K. Knoefel

English Department

12-20-45 E.E.

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STUDIES ON SPINAL ANESTHESIA

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I. INTRODUCTION

Studies in spinal anesthesia have been carried out on two species of animals, the rabbit and the dog. In the rabbit, four drugs, procaine and three new synthetics, have been used and their anesthetic and irritant effects evaluated in an attempt to clarify the relation of these actions. A closely allied problem in man is the infrequent occurrence of undesirable sequelae following spinal anesthesia, including permanent paralyses, cranial nerve palsies and chemical meningitis. In the dog, circulatory disturbances during spinal anesthesia have been followed in the hope that some light could be thrown on the immediate and ultimate mechanism of production. The experimental work is prefaced by a rather complete review of the literature.

II. THE INVESTIGATION OF THE LOCAL ANESTHETIC ACTIVITY OF THREE NEW COMPOUNDS IN THE RABBIT

These compounds will be identified as follows:

- Compound A - β -Dimethylaminoethyl p-aminobenzoate
hydrochloride.
- Compound B - β -Dimethylaminoisopropylphenylurethane
hydrochloride.
- Compound C - β -Dimethylaminoethylphenylurethane
hydrochloride.

Toxicity was measured by subcutaneous injection in mice.

TABLE 1

Compound A	0.6g/Kg	0.8g/Kg	1.0g/Kg		
dead mice					
mice used	4/10	7/10	9/10		
Compound B	1.0g/Kg	1.2g/Kg	1.4g/Kg	1.8g/Kg	2.0g/Kg
dead mice					
mice used	0/10	4/10	2/10	6/10	10/10
Compound C	0.8g/Kg	1.0g/Kg	1.2g/Kg	1.4g/Kg	
dead mice					
mice used	3/10	6/10	6/10	9/10	

Local anesthetic activity was measured by the corneal anesthesia produced by instillation of the solution into the conjunctival sac of the rabbit and by regional infiltration of the nerves supplying the eyelid in the rabbit.

TABLE 2

Anesthetic Applied For One Minute On The Cornea

COMP.	SOL.	EYE	LATENT PERIOD	DEPTH	REFLEX ABOLISHED
A	2%	1.R.	3'	/	23'
		L.	2'	/	27'
		2.R.	2'	/	19'
		L.	2'	/	20'
A	5%	1.R.	2'	/	26'
		L.	2'	/	25'
		2.R.	2'	/	12'
		L.	2'	/	17'
A	10%	1.R.	3'	/	17'
		L.	3'	/	15'
		2.R.	?	/?	9' very lt.
		L.	?	/?	8' very lt.
B	2%	1.R.	4'	/	17'
		L.	4'	/	16'
		2.R.	3'	/	22'
		L.	3'	/	19'
B	5%	1.R.	3'	/	18'
		L.	3'	/	18'
		2.R.	4'	/	13'
		L.	4'	/	13'
B	10%	1.R.	?	/	Very light*
		L.	?	?	Very light*
		2.R.	?	?	Very light*
		L.	?	?	?

* Irritation

TABLE 2 (CONT'D)

COMP.	SOL.	EYE	LATENT PERIOD	DEPTH	REFLEX ABOLISHED
		1.R.	4'	/?	?
		L.			
C	2%	2.R.	?	/?	?* **
		L.	?	/?	?* **
		1.R.	3'	/	9'
		L.	3'	/	14'
C	5%	2.R.	3'	/	7'
		L.	3'	/	6'
		1.R.	?	?	?*
		L.	?	?	?*
C	10%	2.R.	?	?	?*
		L.	?	?	?*

* Irritation ** Eye closed

TABLE 3

Procaine hydrochloride was applied on the cornea in the same manner as a standard of comparison.

COMP.	SOL.	EYE	LATENT PERIOD	DEPTH	REFLEX ABOLISHED
		1.R.	1'	//	15'
		L.	1'	//	17'
Proc.	2%	2.R.	1'	//	12'
HCl.		L.	3'	//	15'
		1.R.	1'	///	36'
		L.	1'	///	44'
Proc.	5%	2.R.	2'	///	56'
HCl.		L.	2'	///	135'

TABLE 4

Compound A

Infiltration of 1% Solution

LID	LATENT PERIOD	REFLEX ABOLISHED
1.R.	1'	29'
L.	1'	21' light
2.R.	1'	18' very lt.
L.	2'	16' very lt.

Compound B

1.R.	2'	21'
2.R.	2'	20'
L.	1'	17'
3.R.	1'	19'

TABLE 4 (CONT'D)Compound C

Infiltration of 1% Solution

:	:	LATENT	:	REFLEX	:
:	LID	:	PERIOD	:	ABOLISHED
:	:	:	:	:	:
:	1.R.	:	:	:	Not abolished
:	L.	:	2'	:	9' very lt.
:	2.R.	:	1'	:	30' very lt.
:	L.	:	2'	:	22' very lt.

TABLE 5Procaine Hydrochloride

Infiltration of 1% Solution

:	:	LATENT	:	REFLEX	:
:	LID	:	PERIOD	:	ABOLISHED
:	:	:	:	:	:
:	1.R.	:	1'	:	20'
:	L.	:	1'	:	14'
:	2.R.	:	1'	:	34'
:	L.	:	1'	:	29'

Credit for the above work and for the histological sections of the spinal cord, to be discussed later, is due to Miss R. Shore.

Compounds B and C, also by comparison with procaine hydrochloride, were studied by subarachnoid injection in the rabbit.

A. METHODS

The technique of Bieter, Cunningham, Lenz, and McEamney² was followed. The rabbit was placed in a canvas sling with sideboards, four holes being cut in the canvas for the proper accommodation of the legs, and the legs were then tied together beneath the canvas; thus the animal presented considerable flexion of the lumbo-sacral region.

According to the above investigators, optimum volume for just filling the sub-arachnoid space in the rabbit, up to the level of the cervical region, is 0.2 c.c. per cm. of spinal cord length. This length is obtained by measuring from the inferior occipital protuberance to the lumbo-sacral interval, along the vertebral column. In order to compare the effect of different amounts of drugs, the concentration of the solutions is varied but the volume injected is kept constant. This method is well-adapted to such studies in the rabbit, because of the negligible amount of spinal fluid in this species. Also, all injections were made in the lumbo-sacral interval, since this is the largest and most accessible intervertebral space in the rabbit.

The above authors describe a technique for measuring sensory anesthesia after spinal injections, by means of a respiratory response; i.e., an increase in rate and amplitude with sensory stimulation, using the Harvard inductorium. For the most part, a perhaps

somewhat less refined or more crude method was used in the experiments reported here. Immediately after the injection, which was made with a tuberculin syringe and a one inch 20 gauge needle, the rabbit's legs were untied and tested for the knee jerk while the legs and dorsal lumbar area were tested for sensory anesthesia, a characteristic response being a jumping movement when sensation was still present although knee jerks were absent. A pointed needle was used as a mechanical stimulus. This response was also verified by placing the rabbit on the floor observing the presence or absence of motor paralysis of the hind legs. If positive, the presence of sensation could often be checked by pricking the paralyzed extremities, when an attempt at escape would be made, using the front legs for locomotion and dragging the hind legs; if they were not paralyzed, this was of course only a test for sensation in the area pricked.

TABLE 6

Procaine Hydrochloride 0.75% Sol.

Rabbit #		1	:	2	:	3	:	4	:	5	:
Duration	S	:	:	:	:	0	:	0	:	:	:
	M	:	:	:	:	12	:	12	:	:	:
AVERAGE	S	:	:	:	:	:	:	:	:	:	:
	M	:	:	:	:	12	:	12	:	:	:

TABLE 6 (CONT'D)

Procaine Hydrochloride 1.25% Sol.

Rabbit #		1	2	3	4	5
Duration						
1st.	S		19	17	30	
	M	13 1/2	24	19	32	
2nd.	S	19	16	18		
	M	31	18		20	
3rd.	S		18		19	
	M		20		31	
AVERAGE	S	19	18	17 1/2	24 1/2	
	M	22 1/4	20 2/3	19	27 2/3	

S = Sensory anesthesia

M = Motor paralysis

Duration = Duration of anesthesia in minutes

In all cases, the motor paralysis appears before the sensory anesthesia. The motor paralysis is noticed within thirty seconds after injection, while sensory anesthesia supervenes usually in about two minutes. Thus, although in most cases, motor function and sensation returned at the same time, the motor paralysis was of longer duration because of its shorter latent period. This difference may be more apparent than real because of the method of determining sensory anesthesia. However, if this were assumed to be a real difference, it would tend to confirm the results of Bieter et al., who found that, contrary to the action of procaine and other local anesthetics on other species, in the rabbit, motor paralysis appears before

sensory obtundation. They also found that sensation returned before motor function. This was not confirmed in the work presented here, although with 0.75% concentration, motor paralysis was obtained in the absence of any demonstrated sensory anesthesia.

After these preliminary studies on procaine hydrochloride, Compounds B and C were investigated by the same method.

TABLE 7

:Rabbit # :	1	2	3	4	5	6	7	8
:Comp. B :	S M	S M	S M	S M	S M	S M	S M	S M
:1.25% :	0 5	? 14					18 18	- Perm.
:2.50% :					23 23	24 30		
:Comp. C. :								
:1.25% :	0 *11	0 *8	? *	0 0				
:2.50% :	33 36	27 29	26 30					

S = Sensory anesthesia

M = Motor paralysis

* = Some muscle weakness, but no true paralysis. Knee jerks present in #2.

 = Permanent irreversible effects.

In #2, the stronger concentration was injected prior to the weaker. (Compound C)

A comparison of Table 6 with Table 5 shows that Compounds B and C have less activity as local anesthetics acting on the spinal cord and its nerve roots. Their activity as surface anesthetics and for regional nerve block was also less than procaine, as shown by Tables 1 to 4. Compounds B and C were more irritant than procaine, this

is demonstrated both by their action on the conjunctivae and the irreversible pathologic changes produced in the fiber tracts of the spinal cord upon sub-arachnoid injection.

B. DISCUSSION OF THE MICROSCOPIC SECTIONS

TABLE 8

:	:	:	:
:	<u>Rabbit</u>	:	<u>Days After</u>
:		:	<u>Last Injection</u>
:	2	:	45
:	7	:	51
:	8	:	6
:		:	

All sections were made according to the method of Trowell²⁴ in which the vertebral column is removed in toto, leaving the spinal cord and dura mater in place. The intact structures are placed in 20% neutral formalin and the spinal cord not dissected out for sectioning until one week later. It is claimed that this procedure produces fewer artefacts than any other method.

Rabbit #2 - Marchi and Scarlet Red Stains

Pathologic changes were seen in the cervical and thoracic sections. These consisted of deeply staining areas in the posterior columns, highly suggestive of degeneration. There were no definite changes in the lumbar region.

MARCHI STAIN SPINAL CORD 10X
 RABBIT NO. 2 - THORACIC SECTION
 ARROW POINTS TO REGION OF DEGENERATION

MARCHI STAIN SPINAL CORD 100X
 RABBIT NO. 7 - THORACIC SECTION
 ARROW POINTS TO REGION OF DEGENERATION

SPINAL CORD - THORACIC SECTION

Semi-Diagrammatic Drawing
Showing Region of Degeneration
Which Appears in Microfilm

Rabbit #7 - Marchi, Scarlet Red and Osmic Acid Stains

The same type of changes were found here as in #2 in the cervical, thoracic and lumbar regions, also in the posterior columns. In addition the Osmic acid stain showed areas which did not take any stain, which is indicative of the same abnormality.

Rabbit #8

All sections normal with the same stains.

The rabbits which had received no sub-arachnoid injections showed no apparent abnormalities, with the same sectioning and staining techniques. Several other stains were used on all sections, including Nile blue, Van Gieson, and hematoxylin eosin, but the ones discussed gave the best results.

C. CONCLUSIONS

1. Procaine hydrochloride apparently affects motor nerve roots in the rabbit, more readily than sensory nerve roots.
2. α -Dimethylaminoisopropylphenylurethane hydrochloride and β -Dimethylaminoethylphenylurethane hydrochloride are weaker surface, regional and intraspinal local anesthetics than procaine hydrochloride. They are also more irritant in their surface and intraspinal actions. This leads to the conclusion that the local anesthetic and irritant actions are not related, possibly because different portions of

of the molecule are responsible for each action.

β -Dimethylaminoethyl p-aminobenzoate was not studied intraspinally, but its surface and regional anesthetic activity was found to be less than that of procaine hydrochloride. It was also found to be not irritant upon corneal application. This might indicate that the irritant action of the other two drugs resides in the phenylurethane moiety.

III. INTRAVASCULAR PRESSURE CHANGES DURING SPINAL ANESTHESIA

A. HISTORICAL REVIEW

In the history of spinal anesthesia many and varied explanations have appeared to account for the changes observed in the circulatory system. Papper, Bradley, and Rovenstine¹⁷ summarize the theories advanced to explain the hypotension as follows:

1. Hematogenous intoxication
2. Direct action on medulla
3. Paralysis of adrenal nerves leading to reduced secretion of epinephrine.
4. Anoxia due to decreased pulmonary ventilation.
5. Paralysis of the vasoconstrictor fibers in the anterior roots of the spinal cord.
6. Stagnation in the post-arteriolar bed.

They present a study of 243 consecutive clinical cases,

in which spinal anesthesia was induced by various drugs, procaine, nupercaine, pontocaine, intracaine, and monocaine, and classify the fall in mean arterial pressure according to the following index: 40% of normal up as severe, 20 to 39% as moderate, 1 to 19% as slight. Their results are: 30% severe, 40% moderate, 21% slight, and 9% none. The important observation is made, that the fall in blood pressure began after surgical manipulation in practically all cases. On the basis of their experience, they emphasize the use of ephedrine, the use of oxygen, and the role of the surgeon in the treatment of the hypotension. Evidence in support of theory number 6 (page 11) is presented from a review of the literature and condensed as follows: (1) decreased venous pressure, (2) decreased cardiac output, (3) increased arterio-venous oxygen difference. They state the reverse of these should hold with moderate reduction of blood pressure due to vasodilatation.

In the discussion following the presentation of this paper, Dr. Stuart S. Cullen, Iowa City, made this criticism:

"... It is difficult to reconcile this arteriolar competence with the incompetent post-arteriolar vessels. Must we assume that sympathetic impulses are non-essential to maintenance of tone of the arterioles and essential to maintenance of tone

in post-arteriolar capillaries? The evidence presented does not exclude relative degrees of arteriolar incompetence ... does not seem logical to assume 'vasomotor defense' is lodged entirely in the post-arteriolar bed in view of anatomic evidence of rich sympathetic supply to arterioles."

Reply by Papper:

"Our thesis is that arteriolar dilatation is not an important factor in normal man, not operated on, under the standard conditions of our investigation hypotension is due to drop in cardiac output from failure of circulation in the post-arteriolar bed. In surgery, whether due to superimposed arteriolar vasodilatation or failure of arteriolar constriction beyond normal tone, I can't say."

"We suggest the fall in blood pressure is due to reduction in cardiac output in consequence of venous stagnation. This is essentially the interpretation of Gray and Parsons. Their emphasis on the venous side follows the long-established precedent of Yandell Henderson."

In reviewing the above work, it should be mentioned that one outstanding difference in man and animals was recorded, namely, the response to CO₂ anoxia and postural changes. According to Smith and associates^{2,3} in animals under spinal anesthesia, there is a characteristic "inverted" response to these agents, which they state, are in unanesthetized animals pressor stimuli. In man, however, they tried all these methods of producing the inverted or depressor response without success, although no pressor response was obtained. This would seem to indicate the dangers of drawing analogies

between the two in certain aspects of spinal anesthesia.

Goodman and Gilman⁸ cite the above report and say, in essence, that the hemodynamic evidence is logically considered, but that the salutary effect of ephedrin is difficult to explain upon the basis of venous stagnation. They believe that a final solution of the problem awaits many determinations of venous pressure and cardiac outputs, under spinal anesthesia.

It seems to this reviewer, that, Seevers and Waters²¹ have made a wise statement when they say that the whole question is extremely complex and the circulatory changes are a resultant of many forces, no one of which should be emphasized to the exclusion of any other. Certain aberrant phenomena, accompanying and occurring as sequelae of spinal anesthesia, among which may be mentioned nausea and vomiting, permanent paralyses, cranial nerve paralyses and chemical meningitis, have never been satisfactorily explained.^{4,11,12,16}

A cogent argument against the venous stagnation theory is provided by the cardiac outputs of Burch and Harrison⁵ on dogs, in which they found that the arterial pressure declined from 50 to 60% of the control values before the outputs were lowered; although the lowering did bear a relation to the amount of fall in blood pressure, the drop in cardiac output being somewhat proportional to the drop in arterial pressure. The

lowering of cardiac output should precede the hypotension according to the concepts of Smith et al.

The question of sympathetic tonic vasomotor control to the musculature of the forearm has apparently been decided in the affirmative by the experiments of Barcroft and associates.¹ Their results tend to negate the hypothesis, discussed in the early portion of this paper, that the sympathetic nervous system has no normal tonic vasomotor control, but perhaps becomes operative in times of stress. They also show that the hyperemia results from the abolition of vasomotor tone rather than general skeletal muscle tone, and in addition rule out any contributory effect of skin vasodilatation.

In a study of 20 normal individuals, Gregory, Lindley, and Levine⁹ produced anesthesia 22 times by sub-arachnoid injection of either 150 mgm. procaine hydrochloride in 3 c.c. of spinal fluid, or 100 mgm. in 2 c.c. of spinal fluid. Anesthesia to the height of the third rib anteriorly was produced in one, above the nipple in one, and to the umbilicus or above in six, below in two; not reported in the others. In no case was there any severe depression in arterial pressure. The maximal average fall was 7 mm. systolic and 6 mm. diastolic, measured by auscultation in 10. Similar slight changes in the first 12 were reported.

These results have recently been confirmed by other investigators who also used normal subjects (9 altogether) and 150 mgm. doses of procaine hydrochloride.¹³

These reports seem to present the exception rather than the rule; however, they were the largest series found on normal individuals. An example of conflicting results is the publication of Goldfarb, Proviser, and Koster⁷. They found that the average of systolic and diastolic pressure fell in 59 out of 60 cases observed. The amount of fall was 81 mm. to 2 mm of Mercury.

150 mgm. of Procaine hydrochloride was employed in most patients, who consisted of surgical patients, convalescents, and volunteers, as controls. Venous pressure, circulation time, blood volume, pulse rate, and cardiac output (by the acetylene method of Grollman) were also measured. From a statistical analysis of their data, (after Fisher), they concluded that there was a significant fall in cardiac output, pulse rate and venous pressure; and an increase in circulation time associated with spinal anesthesia in man. However, all these tests were not carried out upon all patients. For example, venous pressure was measured in 9, and cardiac output was measured in 10 subjects, since it was not feasible to carry out all tests in all subjects.

Nevertheless, controls were run on all measurements, in order to provide comparisons in the determination of probability that the difference was not due to sampling.

From a consideration of the foregoing evidence, it would seem that it has not yet been definitely established that a moderately high level of spinal anesthesia, produced with a dosage of procaine hydrochloride in the neighborhood of 150 mgm., can result in any but an insignificant hypotension in normal, unoperated man. On the other hand, similar levels obtained with similar dosages of procaine hydrochloride can cause severe hypotension in surgical patients, leading to the logical conclusion that surgery introduces an important factor in the pathogenesis of the hypotension. This factor may be of several components; the apprehension of the patient in facing an operation, the nervous stimulation incident to the trauma of the operation, and the blood loss as a result of the operative procedure. Coincidental with these mechanisms, the vasomotor defense may be depressed by the spinal anesthesia. This conclusion of course rests upon the assumption that the premise stated in the first sentence is correct. This premise may be either confirmed or rejected by future evidence.

Smith, Rovenstine, Goldring, Chassis and Ranges²³

report a series of 21 subjects receiving "high" spinal anesthesia. Because the investigations of Smith & associates introduce some radical new concepts as to the etiology of the circulatory changes observed, namely that the hypotension is due to stagnation in the post-arteriolar vessels, not as a consequence of any interference with tonic control of these vessels but as a result of loss of the massaging effect of the skeletal muscles involved and perhaps some pooling in the splanchnic region, their paper is quoted extensively below.

"These are observations on 21 subjects given high spinal anesthesia, an investigation of the effects of anesthetic denervation in normal man, uncomplicated by surgical intervention, on the circulation with particular reference to the vascular bed of the kidney. It is concluded that under basal conditions, the renal arterioles are distinctly autonomous, in the sense that the renal vascular tone is not affected by anesthetic denervation. Our observations further suggest that the arteriolar bed generally, apart from the skin, possesses considerably more autonomy than is generally attributed to it, sufficient, in fact, in the normal individual supine and at rest, to maintain an essentially normal pressure. We find no evidence of significant arteriolar dilatation during high spinal anesthesia, such reduction in blood pressure as occurs being attributable, we believe, to diminished circulating blood volume in consequence of dilatation of the capillaries, venules, and veins."²³

It is pointed out that the idea of tonic sympathetic activity is based largely upon animal experiments which are seriously complicated by general anesthesia, venous

dilatation, etc., not applicable to normal animals, and certainly not to man. Eighteen subjects, two of which were anesthetized to T2, systolic and diastolic pressures equal to or above control levels. In remaining sixteen, there was some decrease in systolic, diastolic or both. Systolic fell more than diastolic in every instance except except number 18. In all but five, diastolic maintained at 60 mm. Hg. or above, and five did not fall below control level. The average of 14 as given in a table are equal to a drop of -14%.

"The type of blood pressure response observed here is, from the point of view of hemodynamics, not consonant with arteriolar dilatation. The fact that diastolic pressure may not fall at all, that it rarely falls below 60 mm. Hg., and that it invariably falls less than the systolic pressure, is directly opposed to the changes to be expected during arteriolar dilatation. Excluding for the moment any volume changes in the post-arteriolar bed, arteriolar dilatation must in principle reduce the peripheral resistance and therefore at a constant cardiac output, the diastolic pressure; if arteriolar dilatation progresses, it leads to circulatory collapse. Therefore, moderate arteriolar dilatation should lead to substantial increase in pulse pressure at the expense of diastolic pressure. Insofar as increased capillary volume results from the arteriolar dilatation, it can only affect this picture by exaggerating those changes. Opposed to the tendency of arteriolar vasodilatation to lower systolic pressure will be any increase in cardiac output as a result of increased venous pressure. It is conceivable that with moderate dilatation, this pressor factor would balance the depressor"23

In a recent discussion of the return of blood to the heart, Roberts¹⁸ seriously questions the time-honored concept that the mechanical actions of skeletal muscles

on the veins of the extremities, and the valves in the veins themselves, are the most important factors in propelling blood from the capillaries through the veins to the right heart. He reasons against this hypothesis as follows:

1. Skeletal muscles can only force as much blood through the veins as is supplied from the capillaries and arteries, therefore they cannot increase blood flow.
2. If the skeletal muscles act like a pump, they should increase low pressure to high pressure. This does not occur in the veins, since the blood proceeds from an area of high pressure (capillaries) to low pressure (veins).
3. If such massaging action is exerted by the skeletal muscles, as much would be exerted in a reverse direction toward the capillaries, as in a forward direction, toward the right heart.
4. Muscular tone has been held to be important in assisting venous return.
5. Valves are present only in the larger veins, therefore their action in preventing reverse flow is not necessary in smaller veins. Also, it is possible that the action of valves is to keep the blood entering larger veins from tributaries, from flowing in the wrong direction.

6. In man, the erect posture can be held for some two hours with only slight movement of the muscles.
7. Finally Roberts believes that the importance of the heart in the movement of the blood has been underestimated. He thinks it is quite possible for the heart to circulate the blood completely, without the necessity of postulating assistance from skeletal muscle.

Of course, these views are diametrically opposed to those of most standard textbooks and to those of Y. Henderson, as quoted by Gunther, who particularly champions the importance of a venopressor mechanism.

Some evidence has been offered by Gunther¹⁰ et al, that muscle tonus, in man is essential for the maintenance of venous pressure. They state that they have never observed a low venous pressure with a normal intramuscular pressure (which latter pressure they believe due to the presence of tonus, when above 18 mm. saline), nor have they ever observed a low venous pressure without a low level for intramuscular pressure. Also, they have found that injection of human plasma raised, first intramuscular pressure then venous pressure, from low levels to normal or above during surgical procedures in which these levels had declined in the same sequence. Thus they conclude that the loss or recovery of intra-

muscular pressure (muscle tonus) is the primary factor preceeding changes in the venopressor mechanism.

The validity of assuming intramuscular pressure a measure of tonus has recently been questioned¹⁴. Also, from the same authors, proof has been offered that there is no skeletal muscle tone (measured by isometric lever) in dogs anesthetized with morphine and sodium barbitol, thus the effect of lowered muscular tone producing in unanesthetized animals a drop in venous pressure would be questionable.

In this connection, Ornstein¹⁵ has shown that by producing contractions of skeletal muscle by a faradic current, he could raise the venous pressure in normal man. His results with patients in shock and under spinal anesthesia are not extensive enough to permit any conclusions. However, he subscribes to the belief that loss of muscle tone accounts for the lowered venous pressure and ensuing arterial hypotension in spinal anesthesia. It does not seem that this author has remembered that such a procedure as he uses may stimulate afferent nerves sufficiently to produce an increase in rate and amplitude of respiration, which would in turn raise venous pressure to observed heights through operation of the "respiratory pump".

Spinal anesthesia in the dog has been exhaustively investigated by Schneider¹⁹ in Germany. His studies covered two years; fifty-seven dogs were used. Pernoxton was used as a basal anesthetic. The Rein thermostromur was used extensively and blood pressures in the brachial artery recorded optically by means of a Frank capsule. The fall in arterial pressure was a most constant finding with doses of novocaine sufficient to prevent complete vasoconstrictive compensation. Accompanying the fall in pressure was an increased flow in the femoral artery and vein, a decreased flow in the brachial artery and mesenteric artery. No changes in respiration were noted. The kidney showed increased flow from the renal vein but a cessation of urine flow from the ureter. Decrease in muscle tonus was found to be a delayed contributory cause of the circulatory collapse, when the collapse occurred. Muscle tonus of skeletal muscle was measured by loading a muscle with one to two kg. weights so that changes in length caused a change in resistance in an electrical circuit. As a result of his investigations, he is driven to the conclusion that the chief cause of the hypotension is a "bleeding" into the vessels, with a failure of venous return. Progressive decline in muscular tonus is regarded as an important accessory factor. Veritol was found to be the best remedy.

It is interesting to note that pneumoplethysmographic measurements in man under spinal anesthesia of the fingers and toes, showed a compensatory vasoconstriction in the fingers, a vasodilatation in the toes, and no changes in blood pressure and heart rate. Nine normal subjects were used and no surgery was performed¹³.

Schuberth²⁰ prefers to call the symptom complex which at times accompanies spinal anesthesia, shock, because of the "peripheral circulatory insufficiency". This condition, he says, includes hypotension, bradycardia, pallor, cold sweat, indisposition and vomiting. This is quite different from shock due to hemorrhage or trauma, since he found no decrease in circulating blood volume in the rabbit and the cat. Right auricular pressure in the rabbit under spinal anesthesia showed no change or a slight fall with a notable fall in arterial pressure. Measurement of cardiac output (Fick principle) in rabbits and in man (Grollman's method), showed a decrease after spinal anesthesia. Arterial oxygen content and venous oxygen content also were diminished, the latter more than the former. However, arterial oxygen saturation was not decreased. Since the hematocrit was lowered, it was concluded that this caused the decreased arterial oxygen. Vital capacity in man showed no constant change. He thinks there is a displacement of the cellular elements of the blood toward the capillaries.

Another approach to the problem of fall in blood pressure with spinal anesthesia has been used by at least two groups of investigators.^{3,26}

One group who used cats and another group who used dogs had similar results, namely a notable drop in arterial pressure with spinal anesthesia in a control series; while only slight or no fall of arterial pressure took place in another series after complete para-vertebral sympathectomy. The initial pressure before spinal anesthesia was lower than in the control group, which might be expected, since blood pressure can be lowered in animals temporarily by this procedure. Two modifications are suggested by these investigations; one, instead of using two sets of animals, use only one, determining the blood pressure before and after spinal anesthesia, then performing the surgery, and again measuring the pressure under spinal anesthesia; two, after performing the surgery, wait for four to six months until the pressure has risen close to pre-operative levels, then determine if any change occurs in spinal anesthesia.

From this review of the literature it seems clear that the exact physiological changes incident to spinal anesthesia are still to be elucidated. The contributing circulatory factors are so complex that it becomes extremely difficult to follow each one in detail²⁶.

Therefore, in the following study, careful measurements of arterial, venous and right auricular pressures were made in the hope that some pertinent facts could be discovered as to changes in these pressures under the influence of spinal anesthesia.

B. EXPERIMENTAL METHODS

Spinal puncture in the dog has been described as so simple that it is used routinely as a class procedure in pharmacology, or so difficult that laminectomy is performed in lieu of it. In view of these wide differences of opinion and for the purpose of gaining more intimate knowledge of the anatomy involved, several punctures were attempted in dead dogs. These attempts were not particularly informative, and an accurate picture of anatomical relations was not obtained until later, when after several successful spinal punctures and anesthesia, one was unsuccessful. This dog's lumbar spine was dissected out and cleaned. It was found that, unlike the lumbar vertebrae of man, those of the dog exhibited a great degree of overlapping of the spinous processes, this downward curvature of the processes protecting the inter-vertebral space through which the needle should be thrust. This finding indicates that for successful spinal puncture as great a degree of flexion of the vertebral column as possible should be produced and maintained during the operation.

From a total of sixteen trials, twelve spinal punctures were successfully completed. The only criterion for entrance of the subarachnoid space was spinal fluid dripping from the needle. Since all dogs used were anesthetized with intravenous single doses of sodium barbital, 250 mgm/Kg, the attainment of spinal anesthesia was assumed after loss of patellar reflexes, which loss was in all experiments immediately present after true spinal puncture and injection of procaine.

The mean arterial pressure was determined in the first eight dogs by a single arm mercury manometer connected to a needle and syringe by a three-way stopcock. As soon as the femoral artery was entered by direct puncture, without cutting down on the vessel, blood flowing into the syringe forced the plunger back and the cock was turned to connect directly with the manometer. The single arm manometer had previously been calibrated against a double arm mercury manometer. Venous pressure was measured in the femoral vein by the same method, except physiological saline in a graduated tube was employed. In both instances, zero pressure was taken against the atmosphere with the needle at arterial and venous levels respectively.

Right auricular pressure was measured by exposing the right external jugular vein and introducing a

ureteral catheter until the tip rested in the right auricle. In the first four experiments a curved glass cannula was used instead of a ureteral catheter.

Autopsies were performed after most of the experiments and the position of the catheter determined. In all instances the tip was lying in the right auricle or at the junction of the superior vena cava with the right auricle. Zero pressures were measured at the same time against the atmosphere by incising the right auricle widely and flushing out the blood with saline from the catheter.

The last four experiments were carried out with the aid of a kymograph recording arterial pressure in the usual manner, with an arterial cannula in the femoral artery. In the last three, oxygen consumption and respiratory minute volume were calculated from the record supplied by a spirometer attached to the tracheal cannula. The spirometer was kept filled with oxygen.

In the first eight experiments all measurements were carried out with the dog in the supine position, the animals being returned thence after sub-arachnoid injection of the anesthetic agent. Dogs nine and ten were turned to the lateral position just before injection and left there after its completion. Numbers eleven and twelve were injected while in the supine

position. This was accomplished by placing the dogs on a table with an open center throughout its whole length.

Mongrel dogs of rather constant size were used. It was found that spinal puncture was performed more easily on the larger dogs. In most experiments 4 hours elapsed between induction of general anesthesia and spinal anesthesia.

C. RESULTS AND DISCUSSION

The most striking result, as taken from an analysis of the data presented in Table 9, is an apparently anomalous finding of no change at all in mean arterial pressure in two experiments; while in two others, the dogs died, one after fifteen minutes and the other after eighty minutes, evidently because of spinal anesthetic, since the blood pressure dropped to 40 mm. Hg. in one and to 38 mm. Hg. in the other from initial levels of 124 and 115. The deaths were presumed to be due to circulatory failure inasmuch as respiratory movements were present up to the moment that the heart ceased beating. On another occasion this low level was reached without a fatality, but the pressure was 78 mm. Hg. before injection, 22 mm. lower than any others in the series.

Alterations in venous pressure were found, but in different directions, being raised in seven and lowered in four. In four out of eleven cases, the change was

TABLE 9

:EXP.:	MEAN ART.:	VENOUS :	R. AUR. :	:	:
:DOG#:	PRESSURE :	PRESSURE :	PRESSURE :	WT. :	DOSAGE :
:	mm. Hg. :	mm.Sal. :	mm.Sal. :	Kg. :	Pr.HCl.:
:	Pre.:Post.:	Pre.:Post.:	Pre. : Post.:	:	:
1	108 : 108	65 : 116	0to12 : -8to0	21.7	3.6 cc.: 5% sol.:
2	124 : 114	72 : 84	0to15 : 0to10	22.3	3.2 cc.: 10% sol.:
3	118 : 84	137 : 100	5to20 : --	22.2	2.5 cc.: 10% sol.:
4	105 : 105	73 : 88	-10to/10:-5to/5	19.2	250mgm 2cc.: Sp.F.-Sal.:
5 ^a	138 : 50	130 : 52	-- : --	27.7	2.5 cc.: 10% sol.:
6	108 : 82	100 : 70	-10 : -20	18.7	250mgm in: 2cc Sp.F.:
7	142 : 88	65 : 63	12 : -25(1) 10(2)	18.8	400mgm in: 2cc Sp.F.:
8 ^b	124 : (1)45 (2)40	72 : --	-- : --	25.6	300mgm in: 2cc Sp.F.:
9	78 : (1)57 (2)36	76 : 137	-15to-13: -5	19.9	300mgm in: 3cc Sp.F.:
10 ^c	115 : (1)52 (2)38	(1)62 (2)57	-2 : --	25.3	300mgm-2.8: cc Sp.F.:
11 ^d	100 : 87	44 : (1)55 (2)44	No zero reading 2mm elevation Post.:	18.9	* :
12	134 : 110	75 : 80	(1)-3 : -4to-6 (2)/3	19.8	300mgm in: 2cc Sp.F.:

a. Considerable blood loss produced.

b. Exitus 80 minutes after injection.

c. Exitus 15 minutes after injection.

d. Explained in detail by graph.

* 2.4 grams total Procaine Hydrochloride - 7 doses.

not significant, amounting to only 5 mm. saline in either direction. Even less significant were the changes in right auricular pressure. Thus it appears that it cannot be decided from the data whether venous or right auricular pressures are raised or lowered in consequence of spinal anesthesia, or for that matter whether there is ever any change. Possibly a larger series would be more informative.

The importance of anoxia as an etiological factor in the hypotension of spinal anesthesia has been variously stressed.⁶ A priori, one would think that the mechanism should be as follows: No effect until the level of anesthesia involves most of the intercostal nerves to give a paralysis of thoracic respiration. Schubert (loc. cit.) has shown by measurements in the rabbit and in man that this paralysis does not necessarily result in a diminution of tidal air. Thus if we assume that increased excursions of the diaphragm compensate for the thoracic respiratory paralysis, at this stage there will not be anoxic anoxia present. However, if the anesthetic level rises high enough to involve the phrenic nerves, complete respiratory paralysis will ensue, precipitating circulatory failure, probably through both direct anoxemia of heart muscle and of medullary centers. It has been demonstrated by numerous

workers that artificial respiration will restore the circulation after the collapse resulting from perfusion of the cisterna magna with procaine. This finding supports such an explanation.

In the series reported here, respiratory minute volume was calculated by measuring volume with a spirometer (previously calibrated with air) filled with oxygen and counting the respiratory rate. This was of course possible only in the last four dogs of the series in which tracings were made with the kymograph and in only two were complete results obtained. Experiment number eleven is unique in that serial injections of procaine were made rather than a single injection as in all the others. The essential findings are illustrated by the graph on the following page. It will be seen that respiratory minute volume did not decrease. Also, the blood pressure was well maintained until the very last. This latter unusual finding is hard to explain, in view of the many separate doses administered. It was necessary to give 600 mgm. of procaine before any appreciable effect could be obtained. After the first 100 mgm., patellar reflexes disappeared, indicating at least a low spinal anesthesia. CoTui (loc. cit.) states that higher doses of intraspinal local anesthetics are required in dogs than in man to

SPINAL ANESTHESIA

Dog No. 11

produce comparable effects. This may be one explanation: the action of the nervous tissue in "fixing" the local anesthetic and the fact that spinal fluid in approximately two cc. amounts were withdrawn each time in order to dissolve the procaine to make the injecting solution, may be another. In any event it is clear that the level of anesthesia never rose high enough to involve the phrenic nerves or medullary centers except possibly after the one gram dose; we were not able to continue the record long enough to see.

In Experiment No. 12 the average of three separate calculations of respiratory minute volume was 4.97 liters. Fifteen minutes after injection r.m.v. was 4.50 liters; nineteen minutes after injection r.m.v. was 4.75 liters. These changes are slight. The fall in blood pressure was only 24 mm., from 134 to 110 mm mercury as can be seen from the tracing. A tracing of Experiment 9 is also presented merely to illustrate general features.

Bradycardia is commonly reported in man with spinal anesthesia. It is not so easily demonstrated in the dog, in fact it is doubtful if it occurs, according to this data: as counted in Experiment No. 9 - 168 before injection, 200 after injection; in Experiment 10 - 168 before injection, 158 after; Experiment No. 8 - 196 after; Experiment No. 4, 186 before, 170 after.

RESPIRATION

BLOOD PRESSURE

300 MG M PROCAINE HCL
IN 2 CC SPINAL FLUID

The impression is gained from these observations that an exact interpretation of vascular and circulatory changes transpiring under spinal anesthesia awaits a more thorough knowledge of the underlying physiology, particularly that of the sympathetic nervous system.

The findings of no change in blood pressure in three experiments are in good agreement with those of Shaw, et.al.,²² who found in six dogs under spinal anesthesia with no general anesthetic, a rise in blood pressure in one, no change in one, and a fall in four.

D. SUMMARY AND CONCLUSIONS

Studies on spinal anesthesia were carried out in the dog. Contrary to the prevailing opinion mean arterial pressure does not always drop as a result of the procedure. On the other hand, similar intraspinal dosages of procaine hydrochloride resulted in the death of two dogs. While this is difficult to explain satisfactorily, it is felt that it must be due to a higher ascension of the drug in the sub-arachnoid space so that it acted on medullary centers, with perhaps an appreciable difference in maintenance of reflex control of circulatory equilibrium as an accessory factor.

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