— President Lecture* —

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Pathological Physiology of Anaphylactic Shock with Special Reference to Circulatory Dynamics

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Attempt was made to analyze the circulatory dynamics in experimental anaphylaxis in order to apply these results to emergency therapy. Interrelation between shock phenomenon and allergic reaction was discussed.

SINCE ACCIDENTS of severe anaphylactoid reactions to penicillin were increased in these ten years, the studies on anaphylactic shock in terms of acute circulatory disturbances became more urgent problem in clinical medicine. The author and his colleagues had published previously several papers on survey of acute fatal and nonfatal severe reactions to antibiotics in Japan¹⁾ and papers on serological and immunological studies of penicillin antibody^{2,3)}. In this paper the author presents the studies on the circulatory dynamics in experimental anaphylaxis of dogs in order to apply these results for the emergency therapy in the clinical cases with acute anaphylactoid reactions either due to penicillin or other drugs.

A. Symptomatology and pathology of anaphylactic reaction to penicillin

Our previous study^{2,3)} revealed that the penicillin anaphylaxis in man was found to be considered as an atopic type of reaction caused by "reagin", a heat unstable skin sensitizing antibody which was found in the majority of the patients with severe imme-

diately reactions. We studied the symptomatology and pathology of anaphylaxis in man by analyzing many cases of penicillin anaphylaxis.

The initial symptoms appeared within a few minutes after medication of the drug, which were consisted of wheal-erythema type reactions of skin and mucous membrane, in addition to these symptoms, constrictive reactions of smooth muscle of bronchi, digestive and urinary organs. Thereafter weak irregular pulse and acute fall of blood pressure were followed by symptoms of acute circulatory collapse such as precordial oppression, wheezing, dyspnea, asphyxia, cyanosis, unconsciousness and convulsions. In most severe cases death may occur in about 15 to 20% of total cases of penicillin anaphylaxis. The clinical feature of penicillin anaphylaxis seems to be superimposed by allergic and shock symptoms. The majority of mild cases may recover after a few hours from their symptoms, while the other may undergo symptoms of delayed shock.

Necropsy findings of fatal cases of penicillin anaphylaxis have been summarized

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by Yoshimura of Tokyo Medico-legal Office (Table I). The outstanding finding was

TABLE I POST-MORTEM FINDINGS IN PENICILLIN ANAPHYLAXIS, SUMMARY OF 15 CASES (YOSHIMURA, TOKYO MEDICO-LEGAL OFFICE)

<i>Edema in Pharyngo-laryngeal Region</i> (6 in lips and 3 in tongue)	10
<i>Increased Secretion in Trachea and Bronchi</i>	12
<i>Lung</i>	
<i>Congestion</i> (Hemorrhage 6)	14
<i>Edema</i>	7
<i>Emphysema</i>	2
<i>Subepicardial Petechiae</i>	5
<i>Spleen</i>	
<i>Congestion</i> (Petechiae 3)	12
<i>Liver</i>	
<i>Congestion</i>	12
<i>Edema</i>	6
<i>Brain</i>	
<i>Congestion</i>	12
<i>Edema</i>	8
<i>Stomach and Intestine</i>	
<i>Congestion</i>	7
<i>Submucous Hemorrhage</i>	1
<i>Edema</i>	1

edematous swelling of the mucous membrane of pharyngo-laryngeal region of upper respiratory tract which may cause acute asphyxia. On the contrary to the anaphylaxis in guinea pigs, emphysema of the lungs were not remarkable while congestion and edema of the lungs were more frequently observed in man. Congestion and edema in various organs, such as in the liver, spleen, brain and digestive tract, were consistently found which might be considered more likely to the usual findings of acute shock death due to any cause.

In summary, pathological studies of human anaphylaxis did not suggest an existence of certain shock organ which were seen in animals characteristically dependent upon the species. It would appear that the peculiar edematous swelling in pharyngo-laryngeal mucous membrane is a characteristic finding in the penicillin anaphylaxis in man which was not observed in experimental animals.

B. Pathological physiology of anaphylactic shock in dogs

The dogs were sensitized and challenged by intravenous injection of horse serum.

a) Circulatory dynamics in anaphylaxis in dogs.

The circulatory dynamics was analyzed by the method of Stewart-Hamilton⁴⁾ using ³²P labeled dog red cells. (Fig. 1)

Fig. 1. Hemodynamics of Anaphylactic Shock.

Within 5 minutes after the challenge by intravenous injection of horse serum, the blood pressure and cardiac output were rapidly reduced, while circulation time was markedly prolonged.

The peripheral resistance could be markedly reduced, which was not able to determine at this phase of shock, consequently resulting in marked reduction of venous return and decrease of the cardiac output.

These findings appeared to be a characteristic feature usually observed in so-called primary shock. In severe cases death may occur at this phase of the shock. Most of

cases recovered slowly from the acute phase in blood pressure and cardiac output, although they did not return to the normal value within 60 minutes after the onset of the shock.

The total peripheral resistance which might have decreased in the acute phase of the shock, showed an increase within 15 minutes up to the higher level than the initial value, in spite of insufficient recovery of blood pressure and cardiac output. These findings suggest that a shift to so-called secondary shock might have occurred.

The decrease of circulating blood volume in anaphylaxis was found to be 10 to 20% of the initial value. However the bleeding of the same amount of blood in control dogs did not induce any significant decrease of blood pressure and cardiac output. Furthermore the mild cases of anaphylaxis showed a significant decrease of cardiac output and marked increase of total peripheral resistance in spite of little decrease of blood pressure.

b) Blood catecholamines.

As shown in Fig. 2, immediately after

Fig. 2. Catecholamines in Arterial Blood in Anaphylactic Shock.

the provocation of the anaphylaxis, an initial increase of epinephrine secretion was observed prior to the marked decrease of systemic blood pressure. A peak of nor-

epinephrine secretion was found at the minimum of the blood pressure curve together with another epinephrine peak. Thereafter peripheral resistance was increased, resulting in an increase of systemic blood pressure, venous return and consequently cardiac output.

In the mild cases with little change in blood pressure, the reactive secretion of catecholamines remained at minimum degree.

c) Electrocardiogram

Depressed ST-T segment and sharply elevated T waves were observed in 7 out of 9 cases. These findings suggest coronary insufficiency and hyperkalemia. Actually plasma K was increased in acute phase of experimental anaphylaxis, but not to such extent which would provoke ECG change. In addition to these findings, A-V block and ventricular extrasystole were occasionally observed. As shown in Fig. 3, in one case with anaphylactic shock due to intravenous injection of thiamine, marked ST-T depression was observed.

Fig. 3. Electrocardiogram in Thiamine Anaphylaxis. (G. I., a 65-year-old man)

d) Extravasation of plasma albumin.⁵⁾

By use of ^{32}P labeled red cells method, the circulating blood volume was found to be gradually decreased after the onset of

anaphylactic shock with a proportional increase of hematocrit value, while the circulating erythrocyte volume remained unchanged. However in the other experiment the distribution volume of Evans Blue was increased up to about 130% of the initial value. This discrepancy between the ^{32}P labeled red cells method and Evans Blue method can be explained by the following interpretation that plasma albumin combined with Evans Blue may leak from the blood vessels in animals with anaphylactic reaction. Actually plasma protein, mainly plasma albumin was found to be decreased after anaphylactic shock, while plasma globulins remained unchanged or increased a little. We compared the prognosis of anaphylaxis, i. e. the survival time after anaphylactic shock in dogs, to the leakage of Evans Blue from the blood vessel or decrease of plasma albumin concentration of 1 hour after the onset of anaphylaxis. There were significant inversed correlations between the prognosis and the leakage of Evans Blue or the decrease of plasma albumin.

TABLE II CHANGE IN PLASMA FRACTIONS AFTER PENICILLIN ANAPHYLAXIS

PATIENT; a 36 YEAR OLD MALE

	After the Onset of the Anaphylactic Shock		
	12 hours	4 weeks	14 weeks
Hematocrit (%)	57.0	50.0	42.0
Plasma Protein (gm %)	6.2	7.0	7.2
Albumin (%)	43.5	52.8	53.2
Globulin			
alpha I	4.1	4.2	5.1
alpha II	5.0	5.8	5.8
beta	10.4	11.5	10.2
gamma	26.2	15.9	14.5
Fibrinogen	10.8	10.8	11.2
Albumin in Whole Blood (gm %)	1.16	1.85	2.23
	(52%)	(83%)	(100%)

As shown in Table II, in one patient with penicillin anaphylaxis, an increase of hematocrit and decrease of plasma protein, especially plasma albumin were found 12 hours after the onset of the reaction. These changes lasted more than 1 month.

There was no correlation between the prognosis of anaphylaxis in dogs and the immediate decrease of blood pressure, while a certain correlation was found between the prognosis and the recovery in the blood pressure after 1 hour.

e) *Erythrocytes and albumin distribution in various tissues by use of radioactive isotope technique.*⁶⁾

In order to determine quantitatively the congestion of blood and extravasation of plasma albumin in various tissues, our colleague Kinoshita⁷⁾ has devised a new method.

By use of this method the quantities of ^{32}P labeled red cells and ^{131}I labeled albumin in the tissue were calculated from the radioactivities measured by the differential counting with Geiger-Mueller counter and scintillation counter.

Marked congestion and more intensive accumulation of albumin were found in the liver tissue of the dogs following anaphylactic reaction, hence this organ was considered as the shock organ in this animal.

Fig. 4. Total Volume of Red Cells (hatched) and Albumin (white) in each Organ in Dog.

Red Cells or Albumin Concentration $\times$ Weight of the Organ. The Red Cells and Albumin Concentration in the Blood before the Shock was arbitrarily set for 100% respectively.

In other organs accumulation of albumin was not so remarkable whereas significant congestion was observed in the spleen, kidneys and heart, comparatively less in the lungs. (Fig. 4) In the tissues of guinea pigs following anaphylactic reaction, accumulation of albumin was observed also significantly in the liver, and less in the lung. In the rabbits, following anaphylaxis, these change were not so significant because the animals might have not survived until the secondary responses could protect the acute phase of the anaphylactic reaction.

Fig. 5. Catecholamines and Corticoids in the Arterial Blood.

f) Other secondary responses

As shown in Fig. 5, the peaks of plasma corticosteroids (compound F and compound B) followed the secretions of catecholamines at the relatively early phase of anaphylaxis. The secretions of corticosteroids did not last so long that the steroids can definitely modify the course of the shock.

No significant changes were observed in Na, Cl. and Ca in plasma during anaphylactic shock. Plasma K was significantly increased, but not to the extent that E. C. G. changes can be induced.

Hyperglycemia was observed somehow parallel to plasma K.

C. Experimental therapy of anaphylaxis in dogs⁵⁾⁶⁾

Intravenous drip infusion of epinephrine for the acute drop of blood pressure in anaphylaxis increased the peripheral resistance resulting in a rapid increase of systemic blood pressure but without satisfactory increase in cardiac output. This treatment did not prevent the extravasation of plasma albumin, consequently with poor prognosis.

Administration of chlorpromazine prior to the challenge alleviated significantly the shock symptoms resulting in a better prognosis.

Administration of antihistamine, tripeleminamine before or after anaphylactic

Fig. 6. Effect of Intravenous Dexamethasone on the Course of the Anaphylaxis in Dogs (Average of 4 cases).

shock in dogs made the recovery of the signs and symptoms significantly faster with prevention of extravasation of plasma albumin.

The most beneficial effect were obtained with treatment by prednisolone and dexamethasone before or after the challenge.

The dogs pretreated with prednisolone

showed a rapid drop of blood pressure and cardiac output as the untreated animals. However the recovery from the primary shock occurred very quickly with a rapid increase of peripheral resistance. Blood pressure and cardiac output returned to the normal values within sixty minutes. As shown in Fig. 6, the same effect was observed with the intravenous injection of dexamethasone after the onset of anaphylaxis.

Dexamethasone protected almost completely the extravasation of plasma albumin which was also confirmed by the radioisotope technique previously mentioned.

D. Summary and Conclusion

The clinical feature of anaphylactic shock in any species appeared to be superimposed by two types of biological responses, namely allergic reactions on one side and shock reactions on the other side. (Table III)

The major allergic responses are consisted of contraction of smooth muscles, and dilatation and increased permeability of blood vessels. The dilatation of peripheral blood vessels, and possibly stimuli of antigen-antibody reaction on the autonomic nervous cen-

ters and also on heart muscle itself may induce decrease of peripheral resistance and venous return, consequently decrease of cardiac output resulting in the primary shock. However patterns of allergic responses are widely different in each species which may characterize the clinical feature of anaphylaxis substantially. For example, acute emphysema and asphyxia due to contraction of smooth muscle of bronchioli is the prominent picture of anaphylactic shock in guinea pigs.

If animals could survive at the stage of the primary shock through a defence mechanism mainly of sympathico-adrenal system they may undergo eventually the secondary shock.

The delayed phase of anaphylactic shock was very similar to the secondary shock in terms of circulatory dynamics.⁸⁾

The extravasation of plasma albumin characterizes the pathophysiological feature of delayed anaphylactic shock and had a great influence on the prognosis of the shock.

The emergency treatment of anaphylactic shock should be directed to overcome the primary shock and to prevent the secondary shock at the same time.

TABLE III
RELATION BETWEEN ANAPHYLAXIS (IMMEDIATE ALLERGIC REACTION) AND SHOCK

<u>HEMODYNAMICS</u>		<u>ANTIGEN ANTIBODY REACTION</u>		
		<i>directly</i>	<i>nervous</i>	<i>humoral</i> (<i>Mediators</i>)
		↓	↓	↓
<u>Primary Shock</u>		<u>Major Symptoms of Anaphylaxis</u>		
	<i>Reduction of</i>	<i>Contraction of Smooth Muscles</i>		
	<i>Peripheral Resistance</i>	<i>Dilatation of Peripheral Blood Vessels</i>		
	<i>Venous Return to the Heart</i>	<i>Increased Permeability</i>		
	<i>Cardiac Output</i>	↓		
	↓	<u>Delayed Anaphylaxis</u>		
<u>Secondary Shock</u>		<i>Extravasation of Plasma Albumin</i>		
	<i>Decrease of Circulating Blood Volume</i>	<i>Decrease of Circulating Plasma Volume</i>		
	<i>Decrease of Cardiac Output</i>	<i>Increase of Peripheral Resistance</i>		
	<i>Increase of Peripheral Resistance</i>	↓		
	<i>Anoxia in Tissues</i>	<i>Secretion of Catecholamines</i>		
		<i>Secretion of Corticosteroids</i>		
		<i>Increase of Blood Sugar</i>		
		<i>Increase of Serum Potassium</i>		

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