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REPORT No. J-188-6 (Final Report)

CONTRACT No. DA - 92 - 557 - FEC - 38659

STUDIES OF RESPIRATORY DISEASES DUE TO AIR POLLUTION IN THE TOKYO-YOKOHAMA AREA

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CONTENTS

Abstract

Part I.

Fifteen normal subjects and eighteen asthmatic patients were tested by spirography and body plethysmography, and changes of airway resistance before and after inhalation of sulfur dioxide in three and six minutes were followed and analysed.

The mean of variation of airway resistance was 1.85 in normal subjects and 2.03 in asthmatic patients, and S.D. of variation of that was ±0.2 in former and ±1.67 in latter. Airway resistance was higher in moderate or severe cases of disease than in mild cases.

Asthmatic patients showed increased sensitivity to sulfur dioxide at 5, 13, 20 ppm in the air during the period of three and six minutes inhalation while no change was recognized at 13 ppm in the group of normal subjects. A correlation between daily variation of airway resistance and daily changes of the atmospheric content of sulfur dioxide was noted in a asthmatic subject.

Part II.

In experimental asthma, change of mechanical properties of the lung of guinea pigs was studied in relation to dose of administered histamine and acetylcholine. Total flow resistance and pulmonary resistance increased abruptly at the time of shock as much as twice of the control value, while pulmonary compliance began to decrease on inhalation with the concentration around one sixteenth of shock concentration and thereafter almost linear relationship was found between pulmonary compliance and logarythm of histamine or acetylcholine concentration.

According to those results, the influence of sulfur dioxide exposure to experimental asthma was studied in guinea pigs, measuring bronchial sensitivity to histamine by the change of total respiratory resistance. However, no significant change of bronchial sensitivity to histamine was observed among the groups exposed. The results give us an impression that the air-pollution might be one of the aggravating factors of bronchial asthma but have little role in the etiology.

STUDIES OF RESPIRATORY DISEASES DUE TO AIR POLLUTION IN THE TOKYO-YOKOHAMA AREA

It has been found in the previous reports[1)2)] that the symptoms of bronchial asthma and chronic bronchitis increase with higher concentration of suspended particles and sulfur dioxide in the air, and moreover, an impression was given that the inhalation of sulfur dioxide increased bronchial sensitivity to acetylcholine in guinea pigs in which changes in mechanical properties of the lung such as lung compliance and airway resistance were measured.

In an attempt to explore the above mentioned results, further investigation has been aimed to clarify, whether airway resistance of asthmatic patients is influenced by the presence of air pollutants in Tokyo (1), and whether the mechanical changes in the lung in guinea pigs induced by histamine inhalation are influenced by the inhalation of noxious agent as sulfur dioxide (2).

PART I. The Influence of Sulfur Dioxide to Asthmatic Patients measured by the Change of Airway Resistance

Pulmonary obstractive disturbance observed on asthmatic patients was measured by spirography and body-plethysmography as well. However, airway resistance measured by body-plethysmography was mainly discussed in this part and also discussed in relation to other parameters measured by spirography.

Materials and Methods

1. Subjects

Fifteen normal subjects and eighteen asthmatic patients were tested by spirography and body plethysmography. Normal subjects were healthy labcratory personels having no respiratory disorder due to specific or non-specific diseases. The asthmatic patients were chosen from the Outpatient Clinic of the Department of Physical Therapy and Medicine, University of Tokyo, School of Medicine. Their sex and age distribution were listed in Table 1 and 2.

2. Methods

1) Spirography was performed using Benedict-Roth Respirometer which capacity was 13.5L and it's recording speed was 44mm/sec. Measured parameters were vital capacity (VC), a percentage of vital capacity to the predicted volume (%VC), forced expiratory vital capacity (FEV), one second volume of FEV ($FEV_{1.0}$) and a percentage of $FEV_{1.0}$ to the FEV (FEV 1.0%).

2) Airway resistance was measured by a body-plethysmograph with Mochizuki's method which was a reformation of DuBois' original method. Applied principle was based on the theory that airway resistance (R) in the ratio of trans-airway pressure (P) during flow to airflow (V).[3)4)] Measuring procedure is stated below.

A subject sits and breaths inside an airtight box, in which pressure of the box is the mirror image of alveolar pressure. If the ratio of alveolar pressure to box-pressure is known, airway resistance will be calculated by measuring airflow and box-pressure. Airflow can be measured directly by pneumotachograph.

In DuBois' original method, airway of pneumotachograph is shut during panting, so that alveolar pressure can be related to the plethysmographic pressure because of no airflow at the moment. On the other hand, in Mochizuki's modified method, an artificial resistance, of which value is known, is inserted between the mouth-piece and the pneumotachograph during panting. Accordingly, resultant phase difference between plethysmographic pressure, i.e. alveolar pressure, and airflow is related to the phase difference occurred when an artificial resistance is removed. Alveolar and plethysmographic pressure can be calculated from such parameters as phase difference, volume, airflow and ambient pressure.

The whole apparatus is shown in Fig. 1. Modified points in the apparatus was as follows.

(1) An artificial resistance was inserted between the mouth-piece and the pneumotachograph, and it was controlled by an operator from outside.

(2) A small air-tight box was placed in front of the face of a subjects sitting in the box. Air in the small box was connected to that of plethysmograph through a tubing of 5cm in diameter and 100cm in length, and temperatur of it was kept at 37°C with vapour saturation. This small box was designed to avoid a deviation of measurement due to the difference of temperature and humidity between exhaled air and air in the box of plethysmograph.

(3) Measurement of airway resistance by Mochizuki's method was done in following principle. A subject sat and was asked to part through the pneumotachograph in the body-plethysmograph. Airflow and the box-pressure were recorded simultaneously on recording paper through the period in which artificial resistance was inserted between the mouth-piece and the pneumotachograph and removed during the fast shallow breathing.

Measurement was carried out at flow rate of 1 l/sec, and a subject was instructed to keep the constant rate of airflow (f) during the examination.

Pulmonary airway resistance (R) is given from the following equation.

$$R = \frac{R_0}{(\tau_2/\tau_1 - 1)} - R_p \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where R_0 and R_p are flow resistance of the inserted artificial resistance and that of the pneumotachograph respectively, and θ_1 and θ_2 are the phase difference between alveolar pressure and airflow at the situation that the resistance is inserted. τ_1 and τ_2 can be given by dividing ΔV_1 and ΔV_2 by the same airflow (f) respectively, where ΔV_1 and ΔV_2 is deflection of box pressure. Fig. 2 shows a sample tracing of the measurement.

5) The method of the inhalation of sulfur dioxide.

The air containing sulfur dioxide was made by mixing with sulfur dioxide gas to the air as shown in Fig. 1. The content of sulfur dioxide in the air was measured by Rosaniline-formaline method[5] quantitatively just before the inhalation, and it's quantity used for this study was 5, 13 and 20 ppm respectively.

The inhalation was carried through the mouth-piece at normal breathing rate and mode, when the contaminated air was flowing out from outlet on 2 l/sec.

4) Measurement of the content of sulfur dioxide in the air in the patient room.

Content of sulfur dioxide in the air in the patient room was measured chemically by Rosaniline-Formalin method. Apparatus and principle was as shown in Fig. 2.

The room air was sucking into the adsorbing bottle with a flow of 1.2l/min, during 30 minutes (36 litre in total). After adsorption of sulfur dioxide in the solution containing mercuric chloride (27.2%) and sodium chloride (11.7%), the content of sulfur dioxide in the solution was determined by photometry and the original concentration of sulfur dioxide in the air was calculated and expressed in ppm.

5) An air purifier (product of Fuji Electric. Co.) was equipped in a patient room. The principle of the air purifier is that suspended particulate matters are adsorbed by the electric discharging method and sulfurized by the electric discharging method and sulfurized matters are adsorbed by an activated charcoal, with a filtration rate of air 10 litre per minute. This apparatus was functioned only in particular days.

Results

1. Variation of airway resistance among normal subjects

Results of spirometry and measurement of airway resistance were listed in Table 1. In the control group, no subject had VC of less than 8% of the predicted value nor $FEV_{1.0}$ of less than 80% of the predicted value, and the values of airway resistance (cm H_2O/L/sec) ranged between 1.5 and 2.4 with a mean of 1.85 (S.D. ± 0.2). This variation of airway resistance in normal subjects seemed to have no relation with sex, age and $FEV_{1.0}$%, although number of cases was small.

2. Airway resistance in asthmatic patients

All results of pulmonary function tests obtained from asthmatic patients were listed in Table.2, in which severity of the disease (graded as mild, moderate and severe), skintest by house dust antigen, latest asthma attack and other clinical references were also shown.

The values of airway resistance in this group ranged between 0.4 and 3.8 (cm H_2O/L/sec) with an average of 2.03 (S.D. ± 1.67). This average value was higher than the control group.

Case distribution was presented according to airway resistance in different groups in Table 3. Values in normal control was mostly distrivuted witnin 2.0 (cm H_2O/L/sec). Therefore all cases were divided into two groups of less or over than 2.0. As shown in Table 3, resistance of almost all of mild cases were in the normal range, while moderate cases were mostly in range of over 2.0.

3. Changes of airway resistance after inhalation of sulfur dioxide in asthmatic patients and normal subjects

Measurements of airway resistance before and after inhalation of the air containing sulfur dioxide were performed in sixteen asthmatic patients and four normal subjects. All subjects inhaled the air containing sulfur dioxide of 5, 13 or 20 ppm during three minutes, and spirometry and airway resistance measurement were followed immediatly after, and then they inhaled again the same air further in three minutes and were tested again in the same way. The results were presented in Table 4, and in Fig. 3.

Airway resistance in the groups of asthmatic patients increased partly when 5 ppm of sulfur dioxide was inhaled three minutes, and this tendency was marked when inhaled six minutes (sum of two successive inhalations with 3~5 minutes interval with inhalation of higher dose of thirteen and twenty ppm of sulfur dioxide all asthmatic patients showed marked increase of airway resistance.

On the otherhand, normal subjects showed no increase of airway resistance by inhalation of 13 ppm of sulfur dioxide for six minutes and of 20 ppm for three minutes.

4. Changes of $FEV_{1.0}\%$ after inhalation of sulfur dioxide in asthmatic patients and normal subjects

Change of the percentage of $FEV_{1.0}$ to the FEV ($FEV_{1.0\%}$) after inhalation of sulfur dioxide in asthmatic patients and in normal subjects were shown in Table 4 and in Fig. 4. In some cases asthmatic group decrease in $FEV_{1.0}$ and in $FEV_{1.0}\%$ after inhalation of sulfur dioxide were seen. There was no apparent correlation between the magnitude of the decrease and the concentration of sulfur dioxide nor the decrease and the duration of the inhalation. No subject in the control group showed decrease in $FEV_{1.0}\%$ after inhalation of sulfur dioxide

5. Daily variation of airway resistance in asthmatic patients comparing with daily changes of content of sulfur dioxide in the air.

Daily changes of airway resistance and $FEV_{1.0}\%$ were followed up in four patients hospitalized in the clinic for 9 to 13 days, and data were compared with daily changes of sulfur dioxide in the air of the patient room. Results were presented in Table 5. Airway resistance in these subjects was not influenced by the difference of weather. Therefore the relationship between the airway resistance and the content of sulfur dioxide in the air shall be analysed simply.
Three of four patients in this study showed their airway resistance values mostly in normal range, (under 2.0 cm H_2O/L/sec). Consequently a comparison between airway resistance and content of sulfur dioxide might not be adequate.

However, patient M. W. (male, 55 of age, slight severe case) showed marked variety of the airway resistance value, and there was a positive correlation between his airway resistance value and sulfur dioxide content in the air as shown in Fig. 5. Correlation coefficient between them was +0.42.

Discussion

The airway resistance among normal subjects was mostly under 2.0 (cm H_2O/L/sec) with small variation suggesting the stable respiratory tract. On the other hand, the airway resistance among asthmatic patients distributed in wide range. The number of cases with airway resistance of more than 2.0mm H_2O was 3 in 9 of mild cases in severity and 6 in 9 of severe cases suggesting a good correlation between the airway resistance and the severity of the disease.

Changes of airway resistance before and after inhalation of sulfur dioxide in short period were marked in the group of asthmatic patients at 5, 13 and 20 ppm in the air respectively, while normal subjects showed no changes with 13 ppm. This suggests that an asthmatic patient is sensitive to sulfur dioxide by inhalation as to acetylcholine or histamine.

Sulfur dioxide in the atmospheric air was thought to influence an asthmatic patient even with the small content as expose period is long.

The airway resistance varied every day in four patients during the period of this study. Three of them were mostly remaining in normal range however. Only one patient showed marked variation during the period reflecting the content of sulfur dioxide in the air. This patient showed a positive correlation between his airway resistance and atmospheric sulfur dioxide content. This is a good evidence that sulfur dioxide in the atmospheric air influences to the obstractive disturbance in an asthmatic patient.

4. In the inhalation test of sulfur dioxide in short period airway resistance of asthmatic patients increased markedly, while $FEV_{1.0}\%$ of same patients showed no significant change. This is probably due to the fact that the measurement of airway resistance is more sensitive than the measurement of FEV which requires the cooperation of the subject.

Summary

1. Fifteen normal subjects and eighteen asthmatic patients were tested by spirography as well as body plethysmography, and changes of airway resistance before and after inhalation of sulfur dioxide in three and six minutes were followed and analysed.

Variation of airway resistance among normal subjects ranged between 1.5 and 2.4 (cm H_2O/L/sec) with a mean of 1.85 ± 0.2 (S.D.), while in asthmatic patients it ranged between 0.9 and 3.8 with an average of 2.03 ± 1.67 (S.D.). Airway resistance was higher in moderate or severe cases of disease than in mild cases.

Asthmatic patients showed increased sensitivity to sulfur dioxide at 5, 13 and 20 ppm in the air during the period of three and six minutes inhalation while no change was recognized at 13 ppm in the group of normal subjects. $FEV_{1.0}$% asthtic patients showed no change when airway resistance varied markedly.

2. A correlation between daily variation of airway resistance and daily changes of the atmospheric sontent of sulfur dioxide was noted in a mild asthmatic subject.

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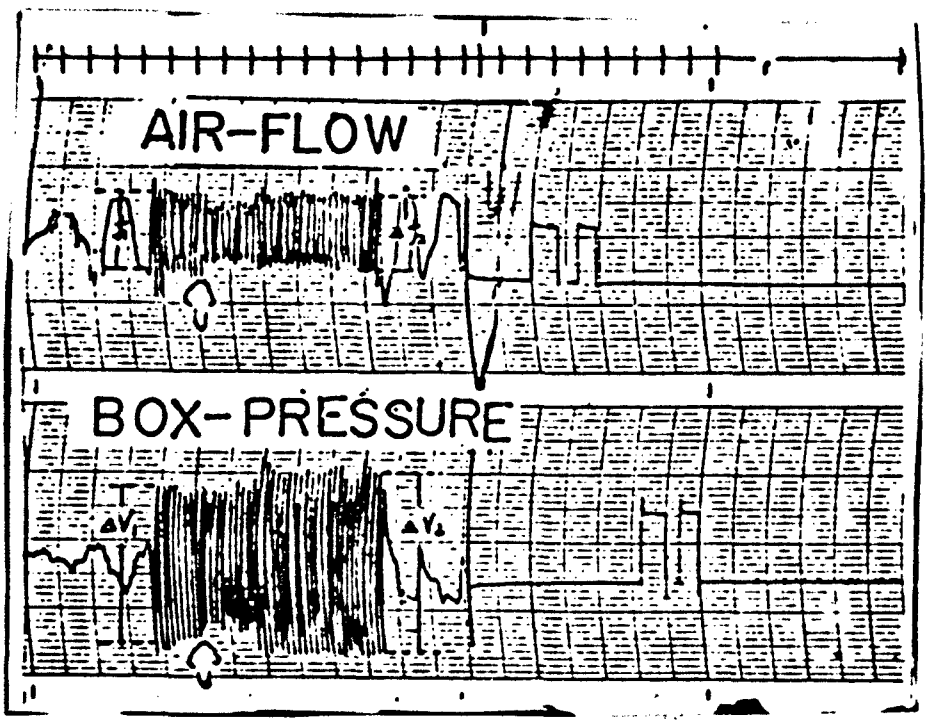
Pic. I Apparatus for Measurement of Airway Resistance

A subject sits inside a body-plethysmograph with its plastic dome open. The body-plethysmograph can be made airtight by closing the dome.



Pic. 2 Simultaneous Recording of Airflow and Box-pressure

During recording on the left side of the arrow an artificial resistance was removed, and during recording on the right side the resistance was inserted. Airway resistance can be calculated from the ratio of V_1 to V_2, in case f_1 is equal to f_2 and the values of from resistance of both an artificial resistance and pneumotachograph are known.

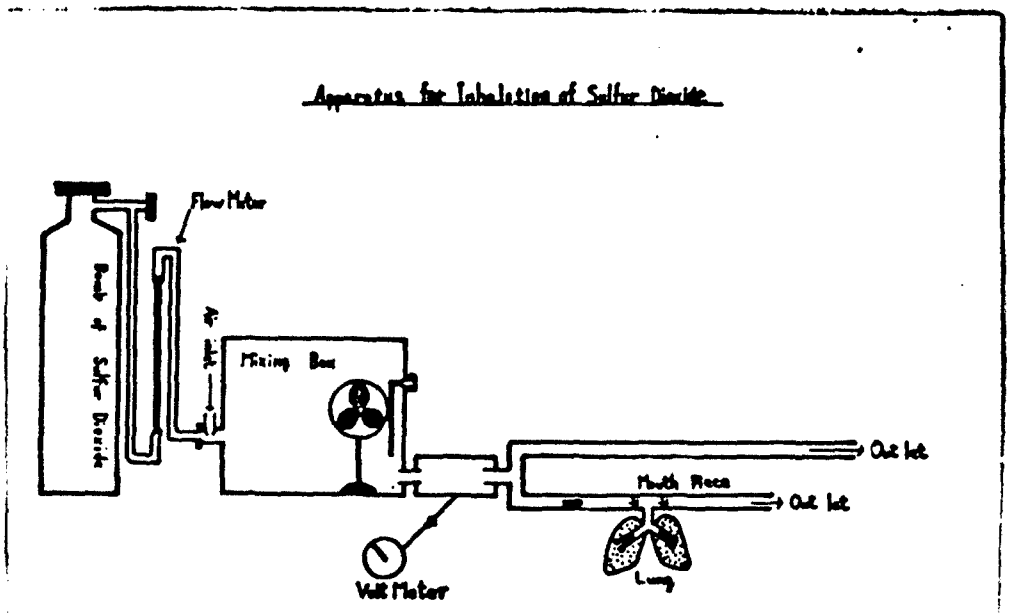


Fig. I The mixing mechanism of sulfur dioxide into the air and inhalation technique of mix the air to man.

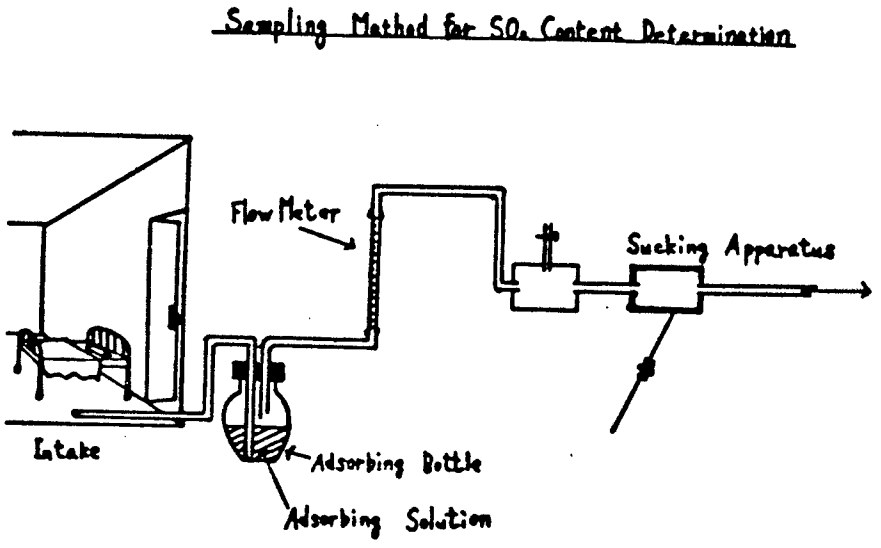


Fig. II The measurement of the concentration of sulfur dioxide in the air the atmospheric air of a patient-room.

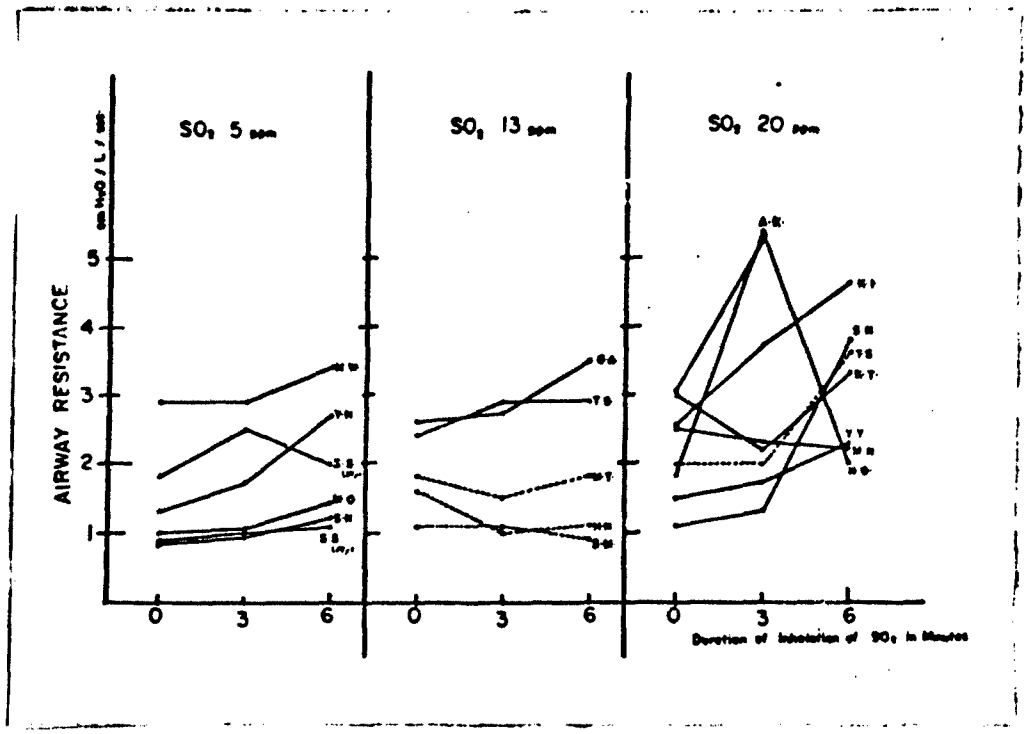


Fig. III Airway Resistance on Asthmatic Patients responded to the Inhalation of Sulfure Dioxide Gas

_____ Patient, ------ Normal Subject

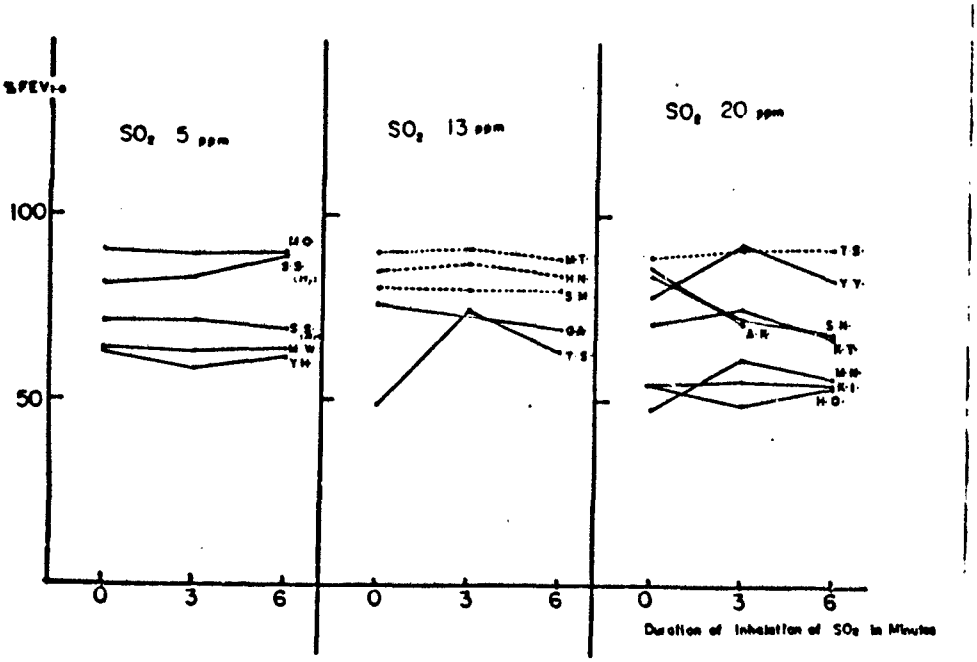


Fig. IV Changes of $FEV_{1.0}$% after Inhalation of Sulfur Dioxide

——— Patient, ——— Normal Subject

Table 1. Results of Lung Function Tests on Normal Subjects

	Sex	Age	V.C. (cc)	FVC (cc)	FEV 1.0 (cc)	% FEV 1.0	Airway Resistance
S.I.	M	16	4150	4000	3680	97.5	1.8
Y.A.	M	16	4400	4320	3880	89.5	2.4
Y.S.	M	17	3810	3680	3440	94.0	1.3
M.N.	M	17	4150	3960	3650	92.0	1.6
S.S.	M	19	3950	4180	3820	91.0	1.9
M.H.	M	26					2.0
M.T.	M	29	4120	3860	3480	90	1.8
H.N.	M	29	4000	3950	3360	85	1.5
S.T.	M	29	4380	4280	3540	82.5	1.8
S.N.	M	30					1.5
T.I.	M	50	3770	3630	3040	84.0	1.8
[illegible].S.	F	22	3410	3440	3060	89.2	1.9
K.N.	F	23					2.0
S.T.	F	30					2.1
R.Y.	F	42					1.8

Average ± SD = 1.85 ± 0.2

Table 2 Resultes of Lung Function Tests on Asthmatic Patients

Subject	Sex	Age	Type	House Dust	Duration of Disease	Grade of Severe-ness	VC (cc)	FVC (cc)	$FEV_{1.0}$ (cc)	% $FEV_{1.0}$	Airway Resistance	
Y.K.	F	20	Inf.	+	3 M	1	2120	2410	2410	100.0	1.5	Typical Asthma Attacks, a Month before
M.K.	F	26	Inf.	+		1	3100	3050	2920	95.5	2.2	Small Asthma Attacks, 2 Days before
M.O.	M	23	Ato.	+	6 M	1	4210	4500	4070	90.5	1.0	
S.S.	M	28	Ato.	+	8 Y	1	3250	2980	2110	71.0	2.8	Asthma Attacks, 3 [illegible] before; Steroid in use
K.T.	M	29	Inf.	+	7 Y	1	4520	4600	3250	71.0	3.8	with Hyposensitization by House Dust Antigen and aurothioglucose.
A.K.	M	29	Mix.	+	7 M	1	3970	3950	3310	86.0	1.5	with Hyposensitization by House Dust Antigen
S.N.	M	39	Ato.	-	11 Y	1	2780	2850	2390	84.0	1.2	with Hyposensitization by Aurothioglucose
S.N.	M	40	Ato.	+	2 M	1	4400	4310	4100	96.5	1.2	Small Attacks, 10 Days before
U.I.	M	60	Inf.	-	1 Y	1					1.5	
T.S.	F	36	Ato.	-	23 Y	2	2500	2710	1320	48.7	2.4	Steroid in use, with Hyposensitization by Aurothioglucose
M.N.	F	43	Ato.	+	20 Y	2	1810	1550	742	47.8	3.3	with Hyposensitization by Aurothioglucose
Y.Y.	M	25	Ato.	+		2	3520	2870	2250	78.2	2.0	Steroid in use, with Hyposensitization by House Dust Antigen
K.I.	M	32	Ato.	+	25 Y	2	4360	3870	2110	54.5	1.4	Steroid in use, with Hyposensitization by Aurothioglucose
H.O.	M	35	Ato.	+		2	3220	3200	1740	54.5	2.7	Steroid in use, with Hyposensitization by House Dust Antigen
S.S.	M	35	Ato.	+	5Y	2	4810	4440	3620	81.5	3.9	
G.A.	M	42	Ato.	+	10 Y	2	2000	1980	1500	76.0	2.6	with Hyposensitization by House Dust Antigen
T.H.	M	50	Mix	+	11 Y	2	3090	3020	1930	63.0	1.3	with Hyposensitization by House Dust Antigen
M.W.	M	55	Ato.	+	12 Y	2	[illegible]	[illegible]	[illegible]			Severe Attack.6 Hours

Table 3. Case Distridution of Airway Resistance between Different Groups of Severity

Airway Resistance (cm H_2O/l/sec.)	Severity of Disease	
	Mild Cases	Moderate Cases
Less Than 2.0	6	3
Over Than 2.9	3	6

Note: One of Severe Case was included in the Column of Moderate Cases.

Table.4. Changes of Airway Resistance after Inhalation of Sulfur Dioxide in Asthmatic Patients and Normal Subjects

Subject	Sex	Age	Content of SO_2 (ppm)	Airway Resistance			% FEV 1.0		
				Before	Inhalating Period		Before	Inhalating Period	
					3 min.	6 min.		3 min.	6 min.
Asthmatic									
G.A.	M	42	13	2.8	2.[illegible]	3.5	76.0		69.7
T.S.	F	36	13	2.4	[illegible].9	2.9	48.7	74.7	63.5
M.O.	M	23	5	1.0	1.[illegible]	[illegible].4	90.5	89.5	90.0
S.S.	M	28	5	1.8	2.5	2.0	71.0	71.0	69.4
S.S.	M	35	5	0.9	1.0	1.[illegible]	81.5	83.2	89.2
S.N.	M	40	5	0.8	1.[illegible]	1.2			
Y.H.	M	50	5	1.3	1.7	2.7	63.0	58.7	61.7
M.W.	M	55	5	2.9	2.9	3.4	64.0	63.[illegible]	64.[illegible]
Y.Y.	M	25	20	1.5	1.7	[illegible].2	75.2	92.5	83.0
K.T.	M	29	20	3.0	2.[illegible]	3.[illegible]	71.[illegible]	75.2	67.5
A.K.	M	29	20	1.8	5.4		86.[illegible]	71.5	
K.I.	M	32	20	2.5	3.7	4.6	54.5	55.5	54.8
H.O.	M	35	20	3.0	5.4	[illegible].[illegible]	54.5	49.2	54.4
S.N.	M	39	2[illegible]	1.1	[illegible].3	3.6	84.0	72.3	68.5
M.N.	F	43	20	2.5	2.3	2.2	47.8	61.5	56.5
Normal									
F.N.	M	29	13	1.6	[illegible].[illegible]	1.1	85.[illegible]	87.[illegible]	84.0
M.T.	M	28	13	1.8	1.5	1.8	[illegible].[illegible]	91.0	88.5
S.M.	M	35	13	1.1	1.1	0.85	80.5	80.0	80.[illegible]
T.S.	F	22	2[illegible]	2.0	2.[illegible]	3.0	89.2	91.5	91.5

PART II.

CHANGES IN MECHANICAL PROPERTIES OF GUINEA PIG IN EXPERIMENTAL ASTHMA INDUCED BY ACETYLCHOLINE OR HISTAMINE

Since the shock organ of guinea pigs is lung and inhalation of aerosols of histamine or acetylcholine causes respiratory changes resembling to the human asthmatic attack. Guinea pigs has been uses to investigate the effects of various drugs for bronchial asthma. Changes of mechanical properties of the lung in experimental asthma was reported almost identical to those in human asthmatic attacks.[2] However, the changes in relation to doses of administered agents has not been well studied.

The aims of this study are (1) to know how mechanical properties of the lung of guinea pigs change in relation to doses of administered histamine or acetylcholine, (2) to know which of measurement will be appropriate to represent experimental asthma.

METHODS

Guinea pigs was anesthetized with ether and a polyethylen catheter 1.2mm D.M. was introduced into the right middle intrapleural space, and placed in the bodyplethysmograph according to Amdurs method[1] as shown in Fig. I. Intrapleural pressure was transmitted to a **pressure transducer** (Sanborn Model 2688) through the intrapleural catheter which was filled with saline solution. Airflow was measured with a mesh flowmeter attached with plastic facemask and Statham differential strain gaige (Model PM 97). Volume was calculated by electical integration of the flow signal with integrator (Sanborn Model 350-3700A). Pressure in the bodyplethysmograph, i.e., pressure applied around the chest of a guinea pig, was measured with Statham differential strain gaige (Model PM ±0.5). Bodyplethysmograph was connected to a oscillating pump which can supply sinewave pressure change of 18 C/S. These signals were amplified with Sanborn Carrier Amplifiers (Model 350-1100B) and recorded on direct recording sistems (Sanborn Model 9641) or displayed on C.R.O. (Sanborn 569B Visoscope). Pulmonary compliance and pulmonary resistance were calculated on recorded tracings following Neergard and Wirz's method. Total flow resistance was read by loops of flow and bodyplethysmograph pressure displayed on C.R.O. which were photographed by Sanborn camera following Mead's oscillating method modified by Swann, et. al.,[4] as described this semi-annual report.

Minute volume, work of respiration, frequency of respiration and ratio of expirium to inspirium were calculated on the recorded tracings. In some experiments we measured approximate changes in chest volume using a pneumograph around the lower thorax.

After recovered from ether ansthesia, aerosols of histamine or acetylcholine solutions was inhaled to a guinea pig for 3 minutes. The concentration of inhaled solutions were doubled serially, ranging from 0.16 to 20.0mg/ml of histamine and from 2.5 to 80.0 mg/ml of acetylcholine. Measurements were carried out immediately after the inhalation. In case pulmonary compliance decreased after an inhalation, the next inhalation was postponed untill compliance value returned to the standard value.

RESULTS AND DISCUSSION

Fig. II shows changes in pulmonary compliance, (C_L) pulmonary resistance, (R_L) total respiratory resistance, (R_T) work of breathing, respiratory frequency, minute volume. ratio of expirium to expirium for various concentration of inhaled histamine. R_L and R_T increased abruptly with histamine inhalation at the time of shock as much as twice the control value, while they presented no definite tendency in change, fluctuating around the control values, until shock occured. Though animals presented dyspneic appearance by increasing dose of inhaled histamine, there was dound frequently no definite increase of resistance, both pulmonary and total. Guinea pigs died sometimes in shock when the resistances increased as to double of control value. Pulmonary compliance began to decrease on inhalation of histamine with the concentration around one sixteenth of shock concentration. Beyound this concentration almost linear relationship was found between C_L and logarythm of histamine concentration. Since compliance began to decrease earlier than other measures, it is considered to be good measurement to represent pulmonary sensitivity to inhaled histamine.

Work of respiration increased gradually in proportion to decrease of C_L and increase of R_L. Though minute volume was kept constant in spite of increasing concentration of inhaled histamine, it began to decrease at the inhalation of shock or $\frac{1}{2}$ of that. It is considered that decrease of minute volume or increase of work of respiration is appropriate to represent dyspnea of experimental asthma, though further comparative work will be needed to clarify the relation between dyspnea and changes of pulmonary functions during the asthmatic attacks of human.

Frequency of respiration changed in preportion to the changes of time constant, e.i., product of C_L and R_L. It was maximam at the concentration of $\frac{1}{2}$ or $\frac{1}{4}$ of shock dose, and began to decrease in accordance to the abrupt increase of R_L. Ratio Exp/Insp increased remarkably at shock, which has been used as a index of experimental asthma.

Though among the measures observed, pulmonary compliance showed the most consistent change for increasing dose of inhaled histamine, its measurement needs to measure the intrapleural pressure the procedure of which hurts animals and consequently on long-term experiments C_L with this method can not adopted for succesive measurement with relative long intervals. In this respect total flow resistance measurement is considered to most appropriate to express experimental asthma, since it increases at shock as definitely as easy to detect and is suitable to be used on long-term follow-up study because it dose not hurts animals. While R_L present the same change as R_L, it can not be used because of the same reason in C_L. Other measures such as respiraton frequency and Exp/Insp ratio changed at the near shock, but their changes did not appear difinite enough to be the index of experimental asthma comparing to those of R_T.

Fig. III shows the change of mechanical properties by acetylcholine inhalation. The methods and presentations are identical to those on histamine inhalation. The results obtained on acetylcholine inhalation were almost similar to those on histamine, though an impression was given that resistance began to increase earlier than in histamine inhalations. Resistance began to increase on acetylcholine inhalation with half of concentration at shock. This result might suggest that in experimental asthma of guinea pigs acetylcholine cause contraction of the bronchi more easily than histamine does.

The concentration at shock ranged from 160mg to 80mg with the mean of 133 in Ach and ranged from 20 mg to 5 mg with the mean of 14 in histamine. The ratio of mean ach concentration to the mean histamine concentration was about 10:1. This ratio was identical to that observed in asthmatic patients which bronchial sensitivity was measured with the minimal dosis to cause 10 percent decrease of FEV 1.0. This finding was interesting to suggest that pharmacological effects of histamine and ach might be similar in the lung of human and guinea pig.

Fig. IV shows changes in chest volume, compliance and resistance in relation to the concentration of inhaled ach. Sometimes resistance decreased temporarily on inhalation at $\frac{1}{2}$ or $\frac{1}{4}$ of the concentration at shock during the course of increasing concentration. In order to understand this phenomenon, as speculation was proposed that this decrease in resistance might come from compensatory increase in lung volume since resistance decreases in large lung volume.[4] Contrary to the speculation, no increase in chest volume was observed on the inhalation in which resistance decreased. In this connection Nadel stated in experiment with cats with histamine injection that the increase in pleural pressure and decrease in compliance will tend to dilate airway and this may account for the decrease in resistance.[2] Further study will be needed to clarify these problems.

Fig. V showed correlation between pulmonary conductance($1/R_L$) and total conductor ($1/R_T$). Correlation coefficients were 0.64 in hist. and 0.69 in ach. both were statistically significant at the level of 1%. This results suggest that measurement of R_T could be used for that of R_L.

SUMMARY

Change of mechanical properties of the lung of guinea pigs was studied in relation to dose of administered histamine and acetylcholine. Total flow resistance and pulmonary resistance increased abruptly at the time of shock as much as twice of the control value, while pulmonary compliance began to decrease on inhalation with the concentration around one sixteenth of shock concentration and thereafter almost linear relationship was found between pulmonary compliance and logarythm of histamine or acetylcholine concentration. Since the measurement of pulmonary resistance and compliance required intrapleural pressure and this procedure hurts animals, measurement of total respiratory resistance is considered to be appropriate to express experimental asthma in long-term studies.

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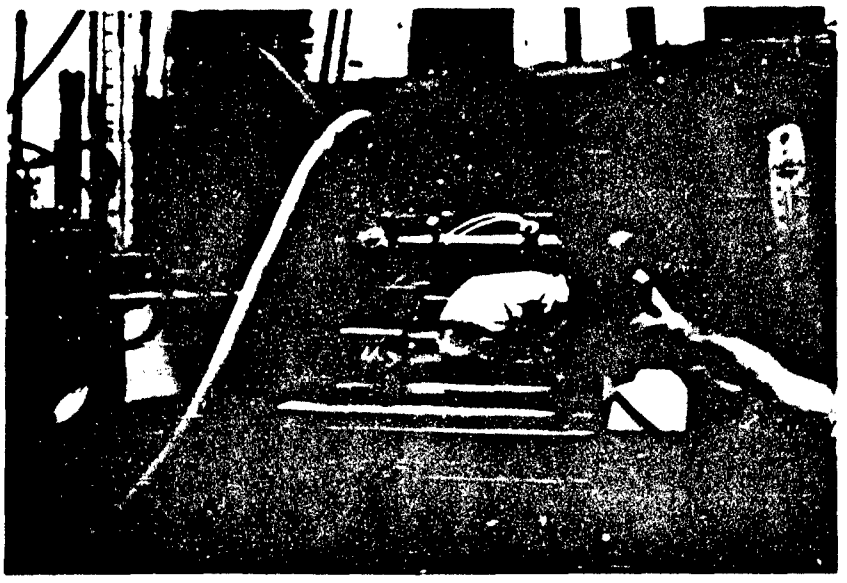

Fig. I Photograph of Apparatus.
A guinea pig was placed in the bodyplethysmograph. A polyethylen catheter was inserted in the pleural space and connected to a pressure transducer. Airflow was measured by a plastic mesch-flowmeter. Box pressure was picked up through front tubing. Oscillating pressure was supplied from a pump through a rear rubber tube.

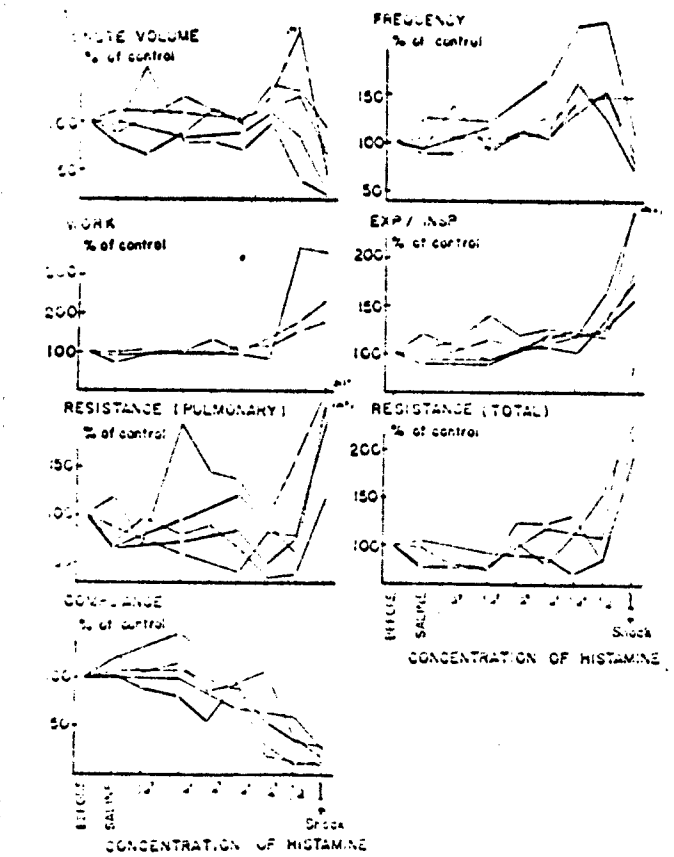

Fig. II

Change of Pulmonary compliance, Pulmonary Resistance, Total Respiratory Resistance, Minute Volume, Work of breathing, Frequency of Respiration. Ratio of Expirium to Inspirium in Relation to Various concentration of Histamine Solution

Measures were expressed as percent of the control values. The concentration of Histamine was expressed as the ratio of concentration where a guinea pig presented shock.

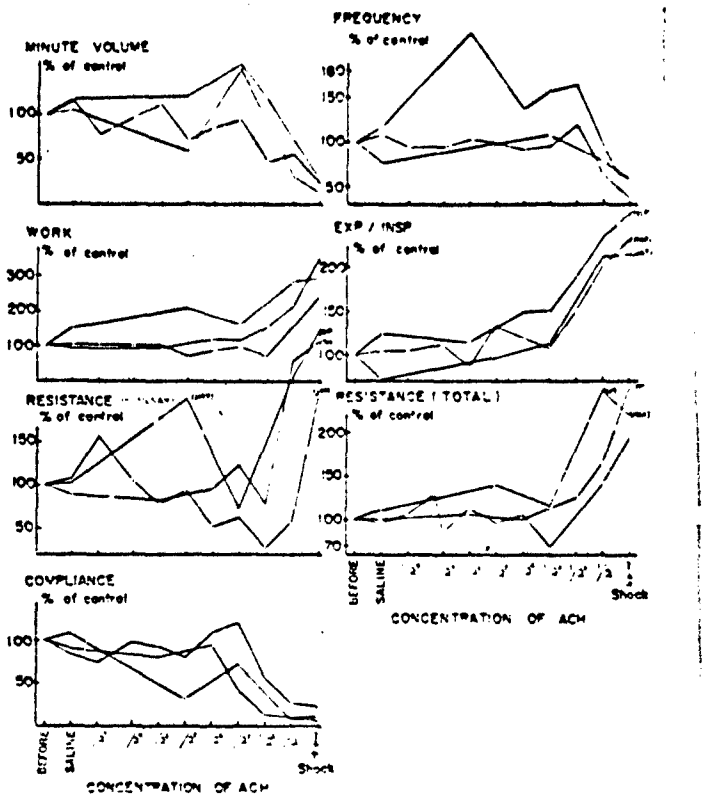

Fig. III Change of Pulmonary compliance, Pulmonary Resistance, Total Respiratory Resistance, Minute Volume, Work of breathing, Frequency of Respiration. Ratio of Expirium to Inspirium in Relation to Various concentration of acetylcholine solution.

Measures were expressed as percent of the control values. The concentration of Acetylcholine was expressed as the ratio of concentration where a guinea pig presented shock.

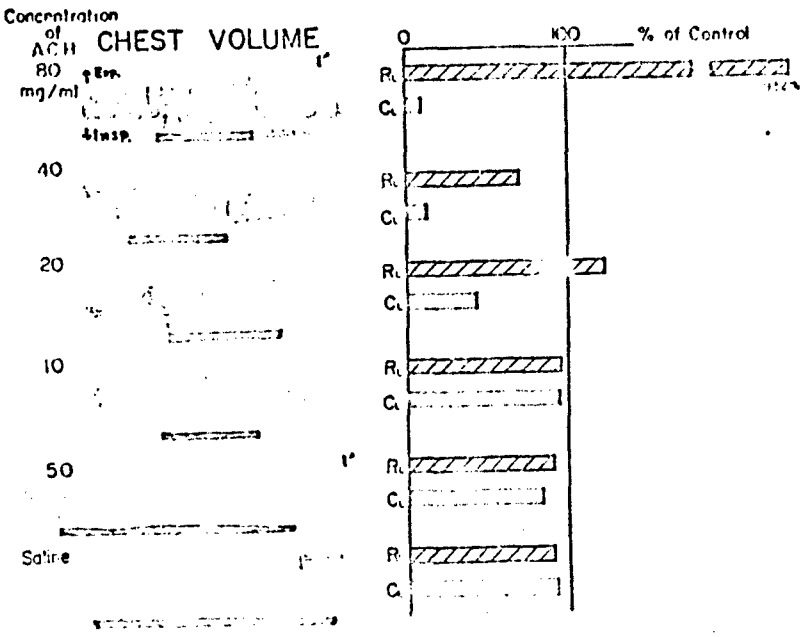

Fig. IV Change of Chest Volume, Pulmonary Resistance and Pulmonary Compliance in Relation to Concentration of Acetylcholine Solution,

Approximate Change in chest volume was measured by pneumograph attached around the lower chest. In inhalation of 40mg/ml of acetylcholine where resistance decreased by 30% of control value, no increase of chest volume was observed.

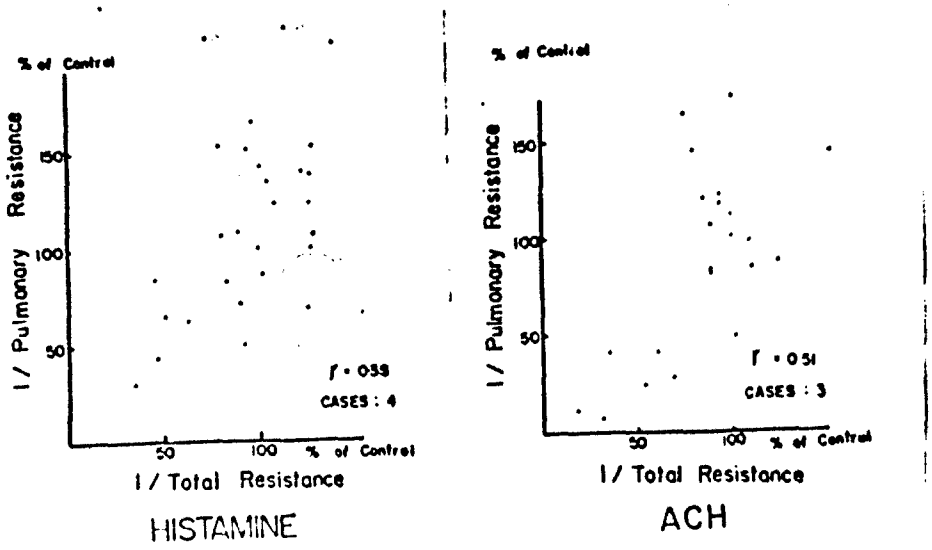

Fig. V Relationship between 1/Pulmonary Resistance and 1/Total Respiratory Resistance.

PART III.

INFLUENCE OF SULFUR DIOXIDE EXPOSURE TO EXPERIMENTAL ASTHMA IN GUINEA PIGS

Sulfure dioxide in the atmosphere of urban area has been considered to be related with increasing frequency of asthmatic attacks. In order to investigate this relation, influence of sulfure dioxide exposure has been studied in various animals. In our previous report sensitivity of the bronchi to acetylcholine was investigated in guinea pigs exposed to sulfure dioxide and not exposed.[2] Though there was found no significant difference of bronchial sensitivity to acetylcholine between them, conclusion has been reserved since experimental asthmatic attack was observed only by the change of alveolar pressure pattern and this method was not quantitative enough.

In this study experimental asthma was quantitatively checked by the increase of total flow resistance. This paper was aimed at knowing whether, in guinea pigs, the exposure to sulfure dioxide accelerates the experimental athma induced by the inhalation of histamine.

MATERIALS AND METHODS

MATERIALS

Male guinea pigs, weighing 250 to 300 g, were used.

METHODS

i) Measurement of total respiratory resistance

Total respiratory resistance was measured by mead's oscillation method modified by Swann et, al..[5] The details in measurement was reported in Semiannual Report of 1965.[3] The principle is as follows: An animal was placed in body-plethysmograph in which sinewave pressure of 18 cycle per second was applied around its chest. Total respiratory resistance was calculated from the ratio of pressure change to resultant flow change.

ii) Measurement of bronchial sensitivity to histamine

As described in Semiannual report of 1965,[3] bronchial sensitivity to histamine was expressed as $H\frac{1}{2}$, i.e., the dose of histamine to cause the increase of total respiratory resistance double of the control value. An animal was allowed to inhale aerosols of histamine increasing their concentration until apparent shock was observed. $H\frac{1}{2}$ was calculated from the dose-response curve.

iii) Exposure to sulfure dioxide

Guinea pigs were exposed to sulfure dioxide with concentrations of 20 and 200 ppm for the period of one hour. Measurement of bronchial sensitivity to histamine was carried out 1) immediately after the first exposure 2) one day after the last exposure of the six daily consective exposures. Sulfur dioxide was supplied from 1.0 percent sulfur dioxide source and its concentration was measured by Rosalinin Formalin method.

RESULTS AND DISCUSSION

Fig II and III show bronchial sensitivity to histamine before and after sulfur dioxide exposure. The mean $H\frac{1}{2}$ of four guinea pigs was 3.32mg/ml before the exposure and after the first one hour exposure the mean $H\frac{1}{2}$ was 4.94mg/ml and after the six daily consecutive exposures the mean $H\frac{1}{2}$ was 10mg/ml, whereas the mean $H\frac{1}{2}$ of four controls were 3.04, 6.4 , and 9.0 mg/ml at each coresponding occasions. The change of $H\frac{1}{2}$ after sulfur dioxide exposure was not statistically significant comparing to that of control group. The mean $H\frac{1}{2}$ of eight guinea pigs was 3.15mg/ml before the exposure and after the first one hour exposure the mean $H\frac{1}{2}$ was 3.46mg/ml and after the six daily consecutive exposures the mean $H\frac{1}{2}$ was 7.62mg/ml whereas the mean $H\frac{1}{2}$ of eight controls were 3.1, 3.22 and 3.66mg/ml at each corresponding occasions. The change of $H\frac{1}{2}$ after the exposure was not statistically significant comparing to that of control group.

These results showed that exposure of sulfur dioxide did not influence bronchial sensitivity to histamine in guinea pigs, taking the apparent increase of total respiratory resistance as a index of experimental asthma. They coincided the results reported in our previous report.[2] As described in our previous report, the polluted atmosphere of the Tokyo-Yokohama area increases the incidence of respiratory symptoms such as coughing, sputum production, throat irritation and pulmonary function disturbances, while there was no increased incidence of airway obstructive diseases.[1)4] It is considered from the results obtained in this study that airpollution including sulfur dioxide might have little part in the ethiology of bronchial asthma, though it causes symptoms in asthmatic patients as shown in the following section of this report.

SUMMARY

The influence of sulfur dioxide exposure to experimental asthma was studied in guinea pigs, measuring bronchial sensitivity to histamine by the change of total respiratory resistance. No significant change of bronchial sensitivity to histamine was observed among the groups exposed to sulfur dioxide, comparing to that not exposed. The results give us an impression that the air-pollution might be one of the aggravating factors of bronchial asthma but have little role in the etiology.

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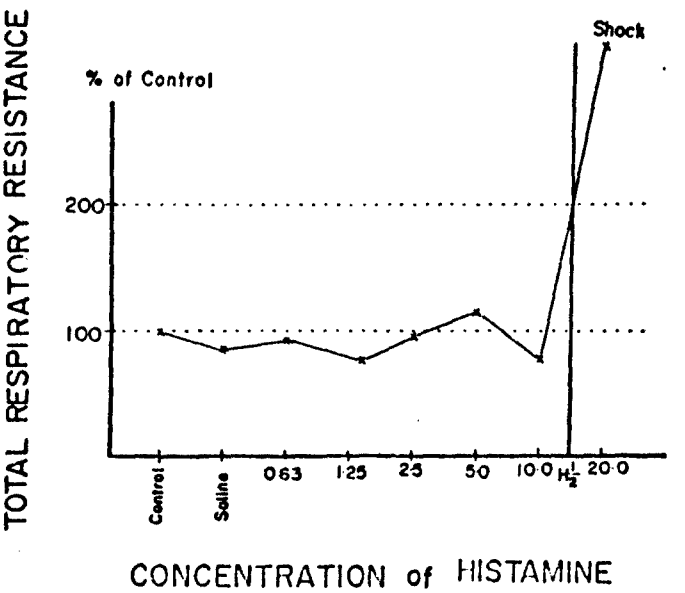

Fig. I: Change of Total Respiratory Resistance in Relation to Concentration of Histamine Solution Inhaled.

Bronchial sensitivity to histamine was represented by $H_{\frac{1}{2}}$, the concentration of histamine solution which was assumed to be required to cause 200 percent increase of total respiratory resistance on the dose - response relation curve.

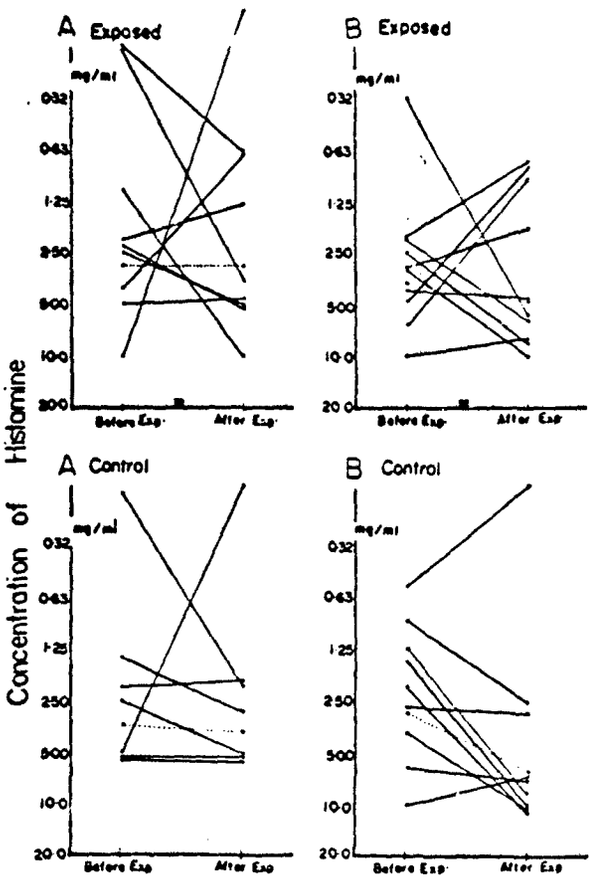

Fig. II. Change of Bronchial Sensitivity to Histamine after Single Exposure of Sulfur Dioxide

(left) Exposure of 20 ppm,
(right) Exposure of 200 ppm.

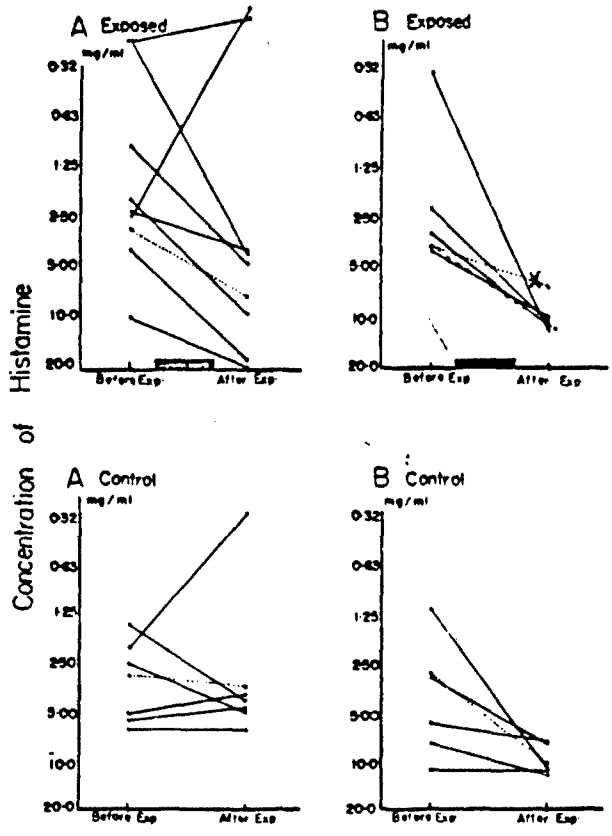

Fig. III. Change of Bronchial Sensitivity to Histamine after 7 Daily Exposures of Sulfur Dioxide

(left) Exposure of 20 ppm,
(right) Exposure of 200 ppm.

According to those results, the influence of sulfur dioxide exposure to experimental asthma was studied in guinea pigs, measuring bronchial sensitivity to histamine by the change of total respiratory resistance. However, no significant change of bronchial sensitivity to histamine was observed among the groups exposed. The results give us an impression that the air-pollution might be one of the aggravating factors of bronchial asthma but have little role in the etiology. (Author)

Unclassified

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DOCUMENT CONTROL DATA - R&D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author)
Department of Physical Therapy & Medicine
University of Tokyo, School of Medicine,
Tokyo, Japan

2a. REPORT SECURITY CLASSIFICATION
Unclassified

2b. GROUP

3. REPORT TITLE

RESPIRATORY DISEASES DUE TO AIR POLLUTION IN TOKYO-YOKOHAMA AREA (U)

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)
Final Report No. 6, 30 September 1965 - 29 September 1966

5. AUTHOR(S) (Last name, first name, initial)

Ishizaki, Tatsushi

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
January 1967	31	16

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
DA-92-557-FEC-38659	J-188-6
b. PROJECT NO. 2N014501B71D	
c. 00 043FE	9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)
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13. ABSTRACT

Part I. Fifteen normal subjects and eighteen asthmatic patients were tested by spirography and body plethysmography, and changes of airway resistance before and after inhalation of sulfur dioxide in three and six minutes were followed and analysed.

The mean of variation of airway resistance was 1.85 in normal subjects and 2.03 in asthmatic patients, and S.D. of variation of that was ±0.2 in former and ±1.67 in latter. Airway resistance was higher in moderate or severe cases of disease than in mild cases.

Asthmatic patients showed increased sensitivity to sulfur dioxide at 5, 13, 20 ppm in the air during the period of three and six minutes inhalation while no change was recognized at 13 ppm in the group of normal subjects. A correlation between daily variation of airway resistance and daily changes of the atmospheric content of sulfur dioxide was noted in an asthmatic subject.

Part II. In experimental asthma, change of mechanical properties of the lung of guinea pigs was studied in relation to dose of administered histamine and acetylcholine. Total flow resistance and pulmonary resistance increased abruptly at the time of shock as much as twice of the control value, while pulmonary compliance began to decrease on inhalation with the concentration around one sixteenth of shock concentration and thereafter almost linear relationship was found between pulmonary compliance and logarithm of histamine or acetylcholine concentration. ( )

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KEY WORDS	LINK A		LINK B		LINK C	
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