GENERAL STAFF MEETING
UNIVERSITY HOSPITALS
UNIVERSITY OF MINNESOTA

CONTENTS

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I. ETIOLOGY, PATHOGENESIS AND CAUSE OF DEATH IN ASTHMA. Abstr. Koucky.

1. ABSTRACT:

PRINCIPLES OF DIAGNOSIS AND TREATMENT OF ALLERGIC DISEASES.

Coca, A. F., J.A.M.A., 97:1201-1203 (Oct. 24) 1931.

Allergy in the current medical sense means the diseases of hypersensitiveness in the human being. Allergic diseases can be tentatively grouped under the headings serum disease, contact dermatitis and atopy. We do not need to define serum disease, with which all are well acquainted. By contact dermatitis is meant a dermatitis due to surface contact with an excitant, typified by the condition formerly known as dermatitis venenata. The known excitants of this condition have been found to be non-antigens.

Since this sensitivity can be demonstrated or induced in a large percentage of human beings (poison ivy, 72%; primulin, 100%, a special hereditary influence cannot be assumed.

By atopy is meant a group of clinical conditions (bronchial asthma, hay-fever, eczema, gastro-intestinal hypersensitiveness and others), which affect a relatively small proportion of the population, about 7%, and which have been shown to be subject strictly to a mendelian hereditary influence. The excitants of this form of hypersensitiveness are usually water-soluble antigens, and when the excitant is an antigen, specific antibodies are regularly demonstrable in the blood with the use of the technic of Prausnitz and Kustner.

In the atopic or inherited group, the skin exhibits a fairly constant and characteristic reactivity (wheal formation) to the introduction of the excitant into the superficial layers through an abrasion (scratch) or by injection.

Some asthmatic subjects react negatively to all known excitants of asthma. The hereditary influence in these individuals has recently been shown by Cooke to be as strong as it is in asthmatic subjects giving positive skin reactions. The cause of the asthma in these persons is sometimes found to be the probably non-specific effect of some infection of the upper respiratory tract.

In spite of fairly definite knowledge of the underlying factors in atopy the results of treatment are variable. Even more striking is the reported infrequent deaths in bronchial asthma. Two deaths in our institution (with necropsies) during the past 6 months seems sufficiently important to bring before our group today for discussion.

2. CASE REPORT

ASTHMA, SINUSITIS.
Path. Pearson.

The case is that of a white female, 39 years of age, admitted to the University Hospitals 11-16-31 and expired 11-18-31 (2 days). (First admitted 8-24-31 and discharged 9-15-31 (22 days). Total stay 24 days.

Asthma (2 years)

12- -29 - Developed coughing spell which gradually cleared up. Remained symptom free until July 1930.

7- -30 - Spell of dyspnea.

8-12-31 - Very severe asthmatic attack which was only slightly relieved by repeated hypodermics of adrenalin and ephedrine. During past two days before admission, she was receiving 1 c.c. of adrenalin, six times daily.

Attack

8-24-31 - Admitted to University Hospitals. Physical examination reveals patient lying on right side. Dyspneic with marked flushed features and marked dilation of the alae nasae. Seems to be in very great distress. Nose - mucous membranes slightly injected. Mouth - tonsils removed; throat is slightly reddened; no drainage from nasopharynx.

Chest examination

Depression of left chest, especially in apical region. States that this has been present for several years. Widening of intercostal spaces and

and emphesematous type. Marked use of the extrinsic muscles in respiration. Hyper-resonant note on percussion. No flatness. Numerous wheezing, music-box rales of high pitched timbre all over chest. Inspiratory phase short and gasping in character with a prolonged wheezing coming with expiration. Breath sounds decreased at bases. No evidence of fluid.

Heart

Pulse 110 to 120. Blood pressure 106/68. Not enlarged to percussion. Accentuation of second sound at mitral area present. No murmurs.

Laboratory

Urine - specific gravity 1.024, sediment negative. Blood - Hb. 106%, wbc 18,350, Pmn's 83%, L 17%. Hemoglobin up, no eosinophiles.

Better - worse

Progress: Marked dyspnea. Given chloral hydrate gr. xv (R), Lugol's solution M xx, in 2 oz. of water. Sodium luminal gr ii (H). Adrenalin M x.

8-25-31 - Several coughing attacks. 250 cc. emesis of greenish fluid. Low protein, high caloric diet. Morphine sulphate gr. 1/6. P to 106. T. normal.

8-27-31 - Atropine sulphate gr. 1/75 for asthmatic attack. Relieved. 3:15 P.M. - atropine sulphate gr. 1/75 again. Says asthma is worse today, on account of rain. 9 P.M. - atropine sulphate gr. 1/75. P 112. T normal.

Pan-sinusitis (x-ray)

8-31-31 - Several asthmatic attacks during day. Adrenalin M vii, six times today. X-ray of sinuses: Marked haziness and irregularity in both maxillary sinuses, the appearance being characteristic of chronic sinusitis. Likewise considerable density in the ethmoidal regions on both sides. Both sphenoids are almost compbetely blocked out, and there is some haziness in both frontal sinuses. Conclusions: Bilateral pansinusitis. Sputum examination - few eosinophiles. Stool - benzidine positive. Urine - negative.

Severe Attack (intensive treatment)

9-4-31 - Very restless. Glucose 50 grams (50%), intravenously. Oxygen started. Insulin x units. Morphine sulphate gr. 1/6. Adrenalin M x. 2:10 A.M. - artificial respiration with relief. One hour later, color good, P 120, R 36. 4:45 A.M. - 35 grams 50% glucose intravenously. Insulin 7 units. Breathing somewhat easier. 8:50 A.M.- 50 gr. 50% glucose, intravenously. Respirations very rapid and labored. 8:55 A.M. - insulin x units. Magnesium sulphate 5%, 5 cc., intramuscularly. Artificial respiration with relief. 10:45 A.M. - Morphine sulphate gr. 1/4. Adrenalin M vii. Still very drowsy and color poor. Hands and feet are cyanotic. Respirations short and shallow. 1:40 P.M. - Oxygen started. Glucose 50%, 40 gr., intravenously with insulin x units. Color is better and less cyanotic. 2:30 P.M. - 8 cc. digitalis given in 3 drams of water per rectum. Artificial expirations for 5 minutes every half hour. Face and hands are cyanotic. 5:30 P.M. - Morphine sulphate gr. 1/8. 8:50 P.M. - 50% glucose, 50 gr., given intravenously with 10 units of insulin, 500 cc. intravenous saline given. 10:30 P.M. - Morphine sulphate gr. 1/8.

X-ray of chest

Medical note: Of the various skin tests, Lamb was the only one that gave a slight reaction. X-ray of chest - Films of the chest made at bedside show considerable increase in intercostal spaces, especially posterior where they are distinctly larger than normal. Diaphragms are low and heart is somewhat centrally placed. Whole appearance suggests emphysema. There is in addition an increase in broncho-vascular markings throughout both lungs. Conclusion: Emphysema. Blood - wbc's 15,600. P to 130. T to 99.8.

Better

9-10-31 - Seems much more comfortable. Takes nourishments. Sits up for about a half an hour. Skin tests applied. Pollens applied, intradermally. Grant and Dwarf Ragweed June grass, and Timothy shows irregular wheals which appeared at end of 10 minutes.

9-15-31 - Discharged. Felt very well.

Submucous resection

11-16-31 - Readmitted to University Hospitals. States she felt very well for 1 month after discharge. Did not have any attacks. On Oct. 15, 1931 again began to develop asthmatic at-

tacks which were very steady. Was slightly relieved by medication. Had a submucous resection done recently.

Admission

Very dyspneic. Oxygen tank started. Sodium luminal gr. ii. 1 cc. adrenalin six times during day. Gets slight relief from medication. Sodium luminal gr. ii again. Magnesium sulphate 50%, 2 c.c. intramuscularly. Morphine sulphate gr. 1/4. Pulse 130. Temperature 99. Respirations 30.

Compression of chest

11-17-31 - Compression of chest during expiration for 5 minutes every hour. Severe asthmatic attacks. 100 cc. emesis of greenish fluid. Morphine sulphate gr. 1/6 three times. Adrenalin 1 c.c. six times. Magnesium sulphate 2 c.c. (50% solution). Very little relief from medications. Sodium luminal i ampule. Magnesium sulphate (50%) 1 ampule. 4 c.c. digitan intramuscularly. Oxygen tent started. Lipiodol injection into sinuses. 20% intravenous glucose started. Breathing very labored.

X-ray sinus

Medical note: Has had 17 hypodermics since readmission for asthma with only partial relief. Medication includes adrenalin, morphine, digitan, magnesium sulphate, sodium luminol. Blood pressure at 12 noon was 128/80. Blood - Hb. 94%, wbc's 15,900, Pmn's 90, L 7%, M 3%. Urine - negative. Right maxillary sinuses injected with lipiodol. To x-ray. X-ray of sinuses - Lipiodol injection of right maxillary sinus shows very marked irregularity characteristic of chronic sinusitis with marked hypertrophy of mucosa and possibly some polypoid formation. Conclusion - Chronic maxillary sinusitis, right. Lipiodol injection of sinuses. Condition was poor following the x-ray. Ate supper after returning toward.

Tight

11-18-31 - Medical note: Condition changed. Chest wall no longer moves (breathing being entirely diaphragmatic). Pressure on chest during expiration no longer forces air out. Abdominal binder applied but did not appear to have any effect. Carbon dioxide at rate of 5 gallongs per hour introduced under oxygen tent with no effect other than to increase cyanosis slightly. A pearl of amyl nitrite was broken and rubbed on the left leg to see if any of the bronchiole spasm would be relieved. Appeared to have no effect.

No response - Exitus

Has had 10 c.c. of digitalis and is now getting 1000 c.c. 10% glucose in normal saline. 4:00 P.M. - Subcutaneous 2000 c.c. normal saline started. 50 c.c. of 50% glucose given slowly, intravenously. Pulse still of good quality but respirations are very unsatisfactory (shallow and spasmodic). Given digitan. 9:35 P.M. - Became worse, respirations more shallow, difficult and irregular. Pulse failed, respirations ceased at 9:40 P.M.

Autopsy

Cyanosis

The body is that of a well-developed well-nourished, white female, 39 years of age, measuring 158 cm. in length, weighing approximately 125 lbs. Multiple puncture wounds in both antecubital spaces. Rigor not present. Hypostasis purplish and posterior. No edema or jaundice. Cyanosis quite marked fingertips and lips. Both pupils are dilated and regular. No special marks.

Peritoneal Cavity shows normal, glistening peritoneum. No fluid. Appendix is subcecal, free, and long - measuring about 15 cm. in length.

Full

Pleural Cavities contain no fluid. Both occupy most all of the pleural cavity and do not collapse when chest is opened. Left lung overlays heart so it can not be seen when the plate is taken off. The Pericardial Sac contains a minimal amount of fluid.

No Hypertrophy

The Heart weighs 250 grams. The valve edges are free and normal. The chambers are normal. No hypertrophy of right ventricle. However, there seems to be dilation of right ventricle and wall seems quite thin and flabby. Muscle is very much congested being very dark red. The Root of the Aorta and coronary arteries show no sclerosis.

Emphysema

The Right Lung weighs 325 grams, Left 290 grams. Both are aboutthe same and

when put in water they float on top. It took quite a bit of pressure to push them down to the bottom. Upon cutting the lungs across, the general texture is rather a pinkish color and numerous mucous plugs can be extruded from the various smaller bronchi and bronchioles. Marked emphysema is present.

No special changes

The Spleen weighs 190 grams. The capsule is grayish. On cut surface, the pulp is of a grayish-brown and trabeculae are somewhat prominent. The spleen is quite firm.

The Liver weighs 1300 grams. There is no evidence of any disease. Some congestion.

The Gall-Bladder and ducts are normal.

The Gastro-Intestinal Tract is normal in its entirety.

The Pancreas (100 grams) and Adrenals are normal.

Each of the Kidneys weigh 175 grams. The capsules strip easily, revealing smooth surfaces. The interior part of the kidneys show no evidence of infection. The pelves, ureters, and Bladder are normal.

The Genital Organs are normal except for prolapse of left ovary.

The Aorta is 4.5 cm. in diameter in the thoracic portion.

Chronic sinusitis

Head. The calvarium and dura are normal. The sinuses are inspected and it is found that the maxillary, sphenoid, and ethmoid sinuses show a thickened mucous membrane (chronic type of infection).

Diagnoses:

1. Asthma.
2. Pan-sinusitis.
3. Submucus resection .(1 month).
4. Pulmonary emphysema.
5. Bronchial mucus plugs.
6. Prolapsed left ovary.

For Microscopic Notes see Footnote #1, Page 419 , 420.

3. CASE REPORT

ASTHMA, NASAL POLYPI, SINUSITIS, SUBMUCUS RESECTION, DEATH DUE TO ASTHMA.

Path. Koucky.

The case is that of a white female, 62 years of age, admitted to University Hospitals 5-1-32 and expired 5-2-32 (1 day).

Asthma (5 years).

5-1-32 - Admitted to University Hospitals. Patient has had asthmatic attacks of increasing frequency for the past five years. She has been treated with morphine and adrenalin without a great deal of relief. The usual treatment for asthma has been carried out in the Out-patient Department but relief was insufficient and patient was very miserable.

Nasal lesion

Examination showed polyps in the nose and deflection of the septum. The maxillary sinuses have been washed at one time in the Out-patient Department and some pus was obtained. It was the intention on this admission to perform excision of the polyps, submucous resection, and following these procedures to explore the posterior sinuses, and if pus was found to do irrigations or promote drainage surgically. These procedures have been recommended because of the possibility of removing a focus for the asthmatic attack.

Physical examination

Past history shows that patient has had occasional attacks of palpitation and dizziness. Health has otherwise been generally good, except for the asthma. Menopause occurred at the age of 62. Physical examination: Nose - deviated septum and spur formation. Tonsils - atrophic. Mouth - wears a dental plate. Eyes - negative. Thorax - no disturbance of respirations; no rales. Heart - rate 80, rhythm regular, no murmurs, blood pressure 128/86. Remainder of examination - negative. Routine bleeding and clotting time - normal.

Attack

5-2-32 - Patient had an asthmatic attack during the night and another lasting about one hour in the morning. 2 P.M. - Luminal gr. i given. 3 P.M. - Luminal 1-1/2 gr.

Operation

3:30 P.M. - Operation. A submucous resection is done. 5:30 P.M. - Patient returned from operating room. Moderate bleeding. Patient complains of a severe headache.

Attack - exitus

8 P.M. - Patient has a severe asthmatic attack. 8:05 P.M. - Ephedrine 1/2 c.c. given. 8:08 P.M. - Adrenalin 1 c.c. given. Patient is extremely cyanotic. Given artificial respiration. 8:10 P.M. - Patient expired.

Autopsy

No special changes

The body is that of a well-developed and fairly well-nourished, white female, 62 cm. in length, measuring 167 cm. in length and weighing approximately 130 lbs. Rigor is present. Hypostasis is purplish and posterior. There is no edema, cyanosis or jaundice. The pupils equal. There are no special marks over the body. The nose is packed with gauze which is bloody. Inspection of the nasal cavity shows operative submucous resection.

The Peritoneal Fluid contains no fluid. The Appendix is free.

The Pleural Cavities contain no excess fluid. There is a small thread-like adhesion in the right apex. The Pericardial Sac is normal.

No hypertrophy

The Heart weighs 250 grams. Examination of the heart in situ shows that the right ventricle is empty and the right auricle does not appear to be dilated. The heart itself appears small. On opening the heart, the right ventricle is approximately the normal thickness and the heart muscle shows no evidences of hypertrophy. The left mitral valve shows a few old thickenings. No recent vegetations are present. The Root of the Aorta and coronaries are normal.

Emphysema - simple asthma

The Right Lung weighs 520 grams, Left 470 grams. Both lungs are very large and emphysematous and feathery to touch. There is no area of atelectasis or bronchopneumonia. There is no interstitial emphysema. Examination of the root of the lung shows no large glands. There are a few soft glands which are somewhat enlarged but nothing to produce pressure on the bronchi. The bronchi are open as far as the bronchi can be opened with ordinary scissors. There is no acute inflammation or plugging of the bronchi. There does not appear to be any thickening or fibrosis of the larger bronchial wall. There is no dilatation of the bronchi.

No special changes

The Spleen weighs 100 grams and shows no abnormal changes.

The Liver weighs 1700 grams and appears normal.

The Gall-Bladder is normal.

Diverticulae

The Gastro-Intestinal Tract shows no disease down to the lower half of the sigmoid colon. From this point on through into the rectum, there are numerous small diverticulae. These are centered quite regularly on each side of the bowel and are about one inch apart. Each diverticulum contains a seed-like fecolith measuring about 1 cm. in length and about 4 mm. in diameter. At one point these diverticulae appear to be inflamed and attached into the culdesac by a few adhesions.

No special changes

The Pancreas and Adrenals are normal.

The Right Kidney weighs 120 grams, Left 150 grams. The kidneys show no disease grossly.

Genital Organs. The uterus, tubes and ovaries are normal except for the left ovary. This contains a yellowish, firm nodule measuring about 2 x 1.5 x 1.5 cm.

The Aorta shows no changes.

There are no enlarged Lymph Nodes except about the hilus of the lung which have been described above.

The Organs of the Neck are not examined

Meningioma

The Head is opened in the usual manner. On the left side just behind the motor area near the falciform is a calcified plaque in the dura with a mass about 2-1/4 cm. in diameter projecting into the cranial cavity (which makes a de-

pression in the brain sufrace). The side of this tumor opposite the dura is soft and grayish, but the center and dural surface is calcified. The remainder of the brain shows no disease which can be made out grossly. The ethmoid and sphenoid sinuses are opened and found to be covered with thick, grayish, slimy and edematous membrane. A great deal of mucus is present in the sinuses but no frank pus is encountered.

Diagnoses

1. Asthma.
2. Pan-sinusitis.
3. Submucus resection (post-operative).
4. Pulmonary emphysema.
5. Meningioma of dura (silent?).
6. Diverticulosis and diverticulitis of colon.

For Microscopic Notes see footnote #2, page 420.

4. ABSTRACT (Cont.)

"Asthma" is derived from the Greek meaning - panting or gasping.

(1) Historical

Condition is described by the Greeks. Thomas Willis (1681) thought it was a disease entity. He described one type due to "cramps" in the bronchial muscles and the other as caused by thick "humors" obstructing the bronchi. Sir John Floyer (1698) gave an accurate description of the disease. Salter (1868) showed the disease was a sound basis. The relation to animal and vegetable emanations was established at this time.

(2) Definition:

Numerous terms are used: "horse" asthma, "pollen" asthma, "bacterial" asthma, "bronchial" asthma, "spasmodic" asthma, and "cardiac" asthma. The word asthma used for convenience to imply a characteristic symptom complex. To use the adjective, attributes to the symptom complex an etiology which rarely is definitely established.

(3) Normal Anatomy and Physiology of Lungs.

For the newer anatomy of bronchi see Miller, W. S., The Harvey Lectures, Series 20:42, 1924-25 and Macklin, C. C., Physiol. Rev., 9:1, 1929. The muscles of the bronchi form a connected lattice-like arrangement just beneath the submucosa. The fibers are generally spiral in direction. No longitudinal muscle is present. As the tubes become smaller, the muscle becomes relatively more prominent. The alveoli and atria have no muscle so that the muscle forms a miniature sphincter at the neck of the atria. The elastic layer is a definite sheet (both circular and longitudinal) between the muscle and mucosa. Mucous glands are present in the larger bronchi.

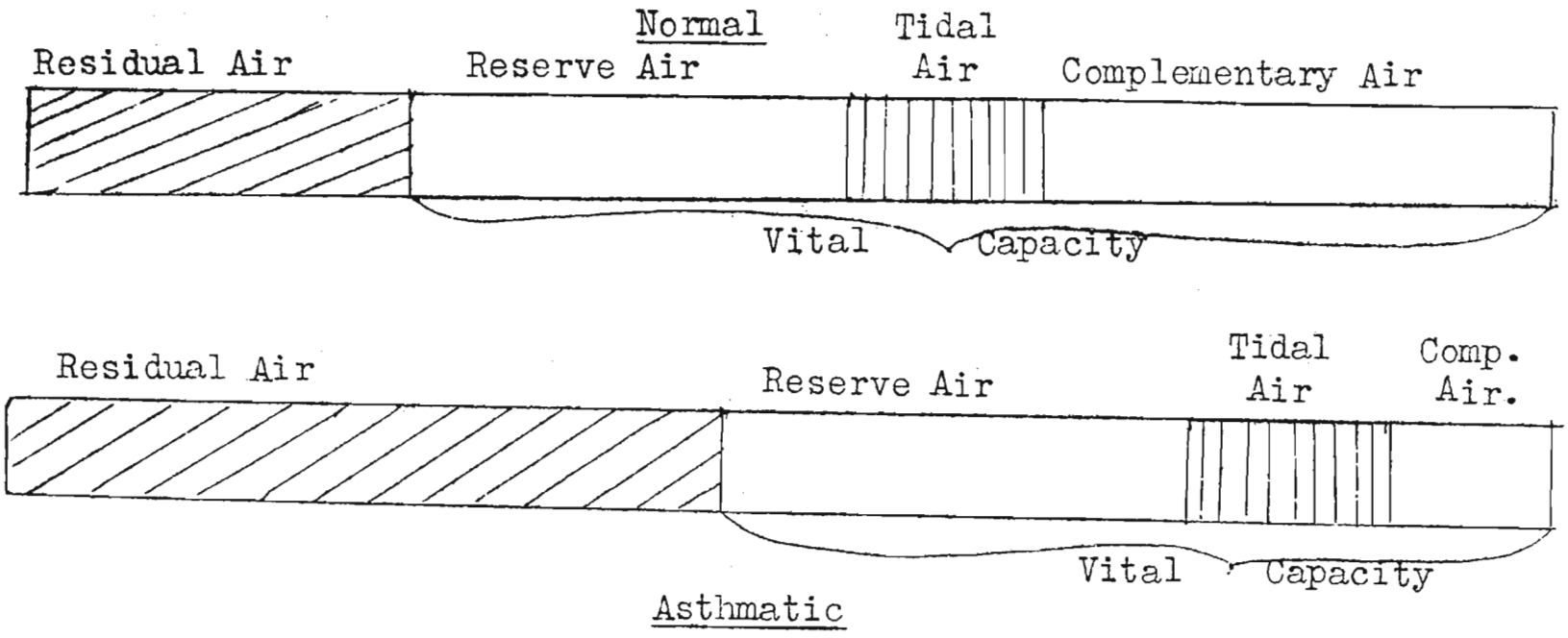
(4) The Movements of the Lungs in Respiration.

With the contraction of the diaphragm and the expansion of the bony thorax in inspiration the negative pressure in the thorax is lowered. Air (and blood) rush into the chest. The bronchi undergo 3 movements: 1. they separate like the ribs in an opening fan; 2. they increase in length, and 3. increase in diameter. These motions are all passive and are dependent on the inflow of air. When inspiration is ended, the recoil of the elastic membrane initiates expiration and the bronchial muscle contraction continues this motion. In expiration the bronchi shorten in length and decrease in diameter.

The Nerves of the lung are the vagi and the upper sympathetics. Their functions are not definitely established. As a general statement open to revision, it may be said that the vagus constricts the bronchial muscles and stimulates the bronchial glands; and the sympathetics relax the bronchial muscles.

(5) The Pathological Physiology of Asthma.

The distribution of air:



The striking changes in asthma are: 1. the reduction in vital capacity; 2. increase of residual air; and 3. diminution of complemental air.

(6) The Effect of bronchial obstruction on distribution of air:

Obstruction may be partial or complete. When it is complete, the air behind the obstruction is absorbed by the blood and the lung in that area becomes atelectatic. When the obstruction is partial, the lung behind the obstruction is distended. Inspiration is carried on by the muscles of the ribs and the diaphragm while expiration is aided only by the muscle and elastic membrane of the bronchi (a much weaker force). Therefore, air can be sucked in past the obstruction but cannot be forced out. Experiments bear this out. When the area under partial obstruction is extensive (asthma or tracheal stenosis) the distension of the lung may be so extreme that the negative pressure in the thorax is destroyed and the pressure may even become positive.

(7) Effect of Modified Thoracic Pressure on circulation:

The flow of blood into the thorax from the periphery is partially dependent on a negative pressure in the chest. When this negative pressure is destroyed or becomes positive, blood flow into the chest (into the right heart) is diminished. The peripheral venous pressure may be increased up to 300%. Under the x-ray, the heart is seen to become smaller and the blood pressure falls. Note: asthmatic complex same as Valsalva experiment.

(8) Effect on blood:

The effect of these difficulties in respiration and circulation on the blood are numerous but all are not understood. Polycythemia occurs and with the increase in hemoglobin there is an increase in the ability of the blood to carry more oxygen. The CO_2 combining power is increased and these patients tolerate increased amounts of CO_2 in their blood. In normals, a concentration of 7.25% causes hyperpnea while in emphysema no change occurs until a concentraion of 9.5% is reached. With this there is an increase in the alkaline buffers of the blood.

There are other blood changes which cannot yet be explained. The amino-acid N is raised (true of all allergic conditions); the blood sugar is lowered andthe Van den Bergh is positive in about 35-40% of cases. The amino-acid N becomes normal between attacks. (Liver function disturbed in asthma?)

(9) Proteose Nitrogen in urine

Is increased during an attack. The nature of the proteose is unknown but reinjection of the recovered proteose in asthmatics reproduces attack but has no effect on normal individuals.

(10) Where and How is Bronchial Obstruction Produced?

Obstruction ofthe bronchi (in asthma) may be produced by: 1. mucus plugs; 2. edema of the mucosa (urticarial-like reaction) and; 3. spasm of the

musculature.

Apparently all 3 obstruction factors occur. After an attack an increased amount of mucoid sputum is raised; at a few autopsies mucus strings were pulled out of the bronchioles (seen in one of our cases) and microscopic sections show mucus plugging of the bronchioles. Edema of the mucosa may be present at autopsy. But the chief feature is believed to be spasm of the musculature. This is based on the sudden onset, the relief by adrenalin and the finding of hypertrophic muscle at autopsy.

(11) How is Bronchospasm Produced?

Why should a systemic allergic condition produce spasm in bronchi instead of in bowel, joints or skin? The allergen is carried by the blood (i.e. it can be injected under the skin, into the lacrymal sac or absorbed from the bowel) and apparently localizes in the bronchioles. This suggests that the bronchiolar walls contain a specific antibody which is not present elsewhere.

Coca thinks that allergic reaction occur in any part which has become sensitized through previous contact with protein: in the bronchioles in asthma; in the skin, in eczema; in the brain in migraine, etc.

Asthma frequently begins after pneumonia or other respiratory conditions. This suggests infectious trauma as the localizing factor. A spasm producing substance in the sputum during asthmatic attacks has been isolated by Harkany. An extract applied to cat bowel causes prompt contraction; that of 56 controls failed to do so.

(12) Anatomic Changes in Asthma:

Autopsies in true uncomplicated asthma are rare. Huber and Koessler collected and studied 21 cases. Rackemann reviewing this series does not accept them as uncomplicated asthma. He accepts only 13 of the 21 cases. Others died with other conditions: heart failure, nephritis, carcinoma of lung, etc.

The reported cases however have been carefully studied.

In general there are two types of asthma pathologically:- 1. simple asthma, and 2. infected asthma (asthma with bronchitis).

(13) Gross Findings:

Type I. The lungs are large and fill the chest. They are soft and feathery. The bronchi may be either normal or fibrotic.

Type 2. The infected type causes the bronchi to stiffen and tends to obliterate the lumen. The lungs are fully expanded but occasionally patches of recent or old atelectasis are present (total obstruction, recent or organized). In either mucus is sometimes found in the medium sized bronchi and can be pulled out ofthe bronchioles like strings.

(14) Microscopically:

The essential features are: 1. thickening of the submucosa by eosinophiles, leucocytes and edema; 2. hypertrophy of the muscles; 3. diminution of the lumen because of the two previously mentioned factors.

Huber and Koessler made numerous measurements of the walls of the bronchioles They found in bronchioles of the same outside diameter the following variations:

	Normal	Asthmatic
Wall thickness	1.00 mm	2.0 mm
Subepithelial thickness	0.11 mm	0.2 mm
Muscle thickness	0.08 mm	0.22 mm

The spasm of the muscle is shown by the marked folding of the epithelial layer? Mucus quite frequently is demonstrated obstructing the bronchioles.

Infection of the bronchi is evidenced in one type of case by sloughing of the epithelium, destruction or hyalization of the basement membrane; lymphocytic and polymorphonuclear infiltrations through the submucosa and fibrosis of the walls.

The part played by the eosinophile is questionable. The number in the blood is increased; the number in the mucosa of the bronchi is enormous. The eosinophiles decrease in the blood during an attack from 2-3% to around .5%. This means that 126 million eosinophiles per liter of blood have probably disappeared from the blood and accumulated in the tissues.

(15) The Heart in Asthma

Kahn believes that the pulmonary emphysema in asthma increased the pressure in the pulmonary artery and "can thus be assumed to have an

effect on the right heart." From E.K.G. studies he found in 50 cases, 20% with right ventricular preponderance. (The type of cases is not stated. Associated disease: chronic emphysema, heart disease, etc. may have been present).

Alexander, Luten and Kosentz studied 50 cases of asthma. In 3 cases there was an independent heart lesion; in 3 others a questionable independent lesion. The size of the heart by orthodiagram was found to be increased only once. Venous pressures in nearly all cases during an attack was increased - sometimes as much as 300%. Vital capacity was reduced in most cases. The blood pressure tended to be low. During an attack the size of the heart was smaller. (Note correlation with previous discussion). E.K.G. studies during an attack showed no right ventricular preponderance and no difference from those taken between attacks. Their impression was "The heart remains singularly free from injury after continuous bronchial asthma despite the attendant emphysema." (Note our 2 cases and case by Drs. Wright and Bell showed no heart enlargement).

Cases however are reported that showed right heart hypertrophy. It is possible that infection superimposed on asthma resulting in sclerosis of bronchi and peribronchial lung tissue may give rise eventually to right heart hypertrophy. In Harkovg's 2 cases, the 1 with signs of infection of the bronchi had hypertrophy of the heart and the 1 with non-infected asthma had a normal heart.

(16) The Pathogenesis and Etiology of Asthma:

The literature on this subject is enormous. No single paper was found that collects all the data and summarized the question. Only a small part of the material therefore can be abstracted here.

Age: 1074 cases (Mass. Gen. Hosp.)

Age	No.	%
0- 9	313	29
10-19	166	15
20-29	202	20
30-39	183	17
40-49	129	12
50-59	59	5
60-up	22	2

Note: Number in each decade up to 50.

Sex: Approximately equal. In the younger groups males predominate.

Family History: 200 cases (Guy's Hosp.) 47% positive. This is striking. Better histories might show more.

(17) Mode of Onset:

	No.	%
Spontaneous	84	42
Respiratory Infection	69	35
Eczema	15	8
Hay fever	10	5
Pregnancy	7	4
Shock	4	2
Intestinal Upset	2	1
Other causes	6	3
	200	100%

Note: large number which are spontaneous and respiratory in origin.

(18) Positive Allergens:

Asthma is generally considered as a manifestation of sensitization to a foreign protein. The skin tests are of scientific interest but are not of great practical value? e.g., Guy's Hospital; "In only about 3% of the patients has it been possible to relieve the asthma by avoiding allergens giving positive skin reactions." This seems an extreme view. (On the whole, the English appear to be disinclined to accept the etiological importance of allergens in asthma). The percentages of positive skin reactions are:-

Mass. Gen. Hosp: 1074 cases - 40%
Guy's Hospital: 200 " - 46%
Leyden: ? - 90%

(19) The Leyden report is of considerable interest. Storm Van Lecuwen works with people from the lowlands of Holland and finds that the most common allergen is house dust composed of human emanations, molds, bacteria, insect emanations, etc. (harbored in moist material). As proof of his contention that this is the cause of asthma, 80% of 800 cases placed in a allergen proof chamber became free of attacks in 3-4 days. This is the so-called "extrinsic" asthma. The proof seems quite clear that in this group there is a definite relationship to an external foreign protein.

(20) The group called by Rackemann "Intrinsic" asthma is composed of cases sensitive to an allergen generated within the body (usually bacterial).

The patient has become sensitized to an infection. Asthma after the common cold is an example. Infections of the nose and throat and respiratory tract are the most important sources of the allergen. The importance of this group is stressed by Rackemann. He is of the opinion that a simple "extrinsic" asthma through the trauma of repeated seizures becomes more susceptible to respiratory infection and becomes secondarily a mixture of extrinsic and intrinsic asthma. This may be the cause of the cases described under types as "infected" asthma.

(21) "Reflex" asthma: a group apparently induced by upsets in the nervous system. The English apparently stress this type more than the other groups. They are impressed by the general nervous instability of asthmatic patients; by the inherited tendency, and "certain constant divergence from the normal": low blood pressure, the changes in the blood chemistry, and the tendency to hypoglycemia, increase of attacks by fatigue (hypo-function of the adrenals), etc.

One form of reflex deserves mention. Stimulation of the mucus membrane of the nasal septum in its upper and back portion causes a contraction of the bronchial muscles. Polyps, etc., irritating this area therefore have been considered a factor in producing asthma.

Cardiac asthma might be another form of reflex. The explanation of this type is not definite. The most frequently cited explanation is that the asthmatic features are reflex from stimuli arising in the aorta? (See Footnote #3, page 420.)

In the Mass. Gen. Hospital series of 1074 patients, the division into etiological types was as follows:

	No.	%
Extrinsic	425	40
Intrinsic	499	47
Unclassified	150	13

"Intrinsic" includes the reflex group and the unclassified are chiefly those with infection superimposed on extrinsic asthma.

(22) Relation of the Nose and Throat to Asthma.

Rackemann reviews the data on this point. In his group of 1074 cases 44% had some focus of infection about the head and 27% had had previous nose and throat operations. Mathews (Mayo Clinic) reported 90% with a focus; Gottlieb, 26%. Previous operations were reported in 30% by Lintz and 49% by Piness.

(23) Treatment:

Dundas-Grant report 39% with great improvement; 42% with some, and no improvement in 19% after operation. Rackemann states that in their group (1074 cases) about the same results were obtained. However, other conflicting statements are collected:- Lintz - "no operation will cure or even benefit asthma"; Piness - 49% of his 834 cases were operated on with no improvement; Kahn - "asthma not influenced" by operation; Heatley and Crowe (Johns Hopkins) in 63 operations had only 1 case "cured." Tod (Edinburgh) reported 10% cure and 49% improved.

One is strongly impressed that the cases probably are mixed allergens - extrinsic asthma with superimposed infection, or intrinsic (bacterial) asthma with infection both in the nose and throat and in the bronchi. Operation therefore improves the patientonly as much as the focus removed played a part in the etiology.

(24) Sudden Death in Asthma:

In abstracting the literature care was taken to try and find an explanation for the sudden death in some cases. The following (from Rackemann quoting Scott, R. W., Arch. Int. Med. 26:544, 1920 is presented as a possible explanation.

The emphysematous patient is able to tolerate larger quantities of CO_2 in his expired air as well as in his venous blood. Meanwhile, the alkaline buffers in the blood rise so that the CO_2-buffer relationship is not changed. Such patients tolerate (without hyperpnea) CO_2 concentrations up to 9.5% (normal limit 7.2%). He remains fairly comfortable up to this point at which time a "break" occurs and the sudden development of dyspnea is "violent and disturbing." This asphyxia is caused by a failure of the respiratory center to respond to the increase in the blood CO_2. (Note our case: returned to room at 5:20 P.M. no symptoms until 8 P.M.; then sudden death with cyanosis and dyspnea.)

(25) Impressions:

1. Allergy (current usage) means diseases of hypersensitiveness in human beings (serum sickness, contact dermatitis, and atopy). Some are not antigenic in nature (dermatitis): others are due to specific antigens (atopy). They disable but seldom cause death.

2. Bronchial asthma (antigenic and hereditary) has been known for a long time. It is a symptom complex rather than a disease entity.

3. Newer concepts of respiratory act include active participation on the part of the bronchi with less certainly about the part the vagus and sympathetic nerves play.

4. Striking changes in the pathological physiology of asthma are: Reduction of vital capacity, increase of residual air, diminution of complemental air.

5. Complete bronchial obstruction causes atelectasis, partial obstruction, emphysema. In atelectasis, the tendency is for intrathoracic pressure to become more negative and in emphysema more positive.

6. When thoracic pressure is modified, certain circulatory changes take place. The blood flow into the right heart is diminished, heart seems to become smaller under the x-ray, and the venous pressure rises (emphysema). In atelectasis, as far as we know, there are no definite circulatory changes.

7. Changes also occur in the blood in asthmatic attacks. Polycythemia develops, CO_2 combining power increases, buffers are increased, amino-acid nitrogen is raised, blood sugar is lowered andthe van den Bergh is positive in a considerable number of cases.

8. During attacks, proteose nitrogen in the urine is increased. Re-injection of the recovered proteose in asthmatics reproduces the attack but has no effect on normals.

9. Obstruction of bronchi in asthma may be due to a mucous plug, edema of mucosa or spasm of musculature. Apparently all 3 participate but spasm is probably the most important factor.

10. Reactions to allergens occur in any part which has become sensitized through previous contact.

11. Asthma may be primary or follow respiratory infection. Infection is thought to be a traumatic influence in localizing the process.

12. Spasm producing substances have been isolated from the sputum of asthmatics.

13. Autopsies on true uncomplicated asthma cases are uncommon. Of the 21 reported cases, only 13 are not open to some criticism. Our second case is an example (dural tumor).

14. There are apparently 2 types, the simple with large, feathery, soft lungs and either normal or fibrotic bronchi, and the infected with stiff, obliterated bronchi and patchy atelectasis. Mucus is a common finding in both.

15. The microscopic features of asthma are thickening of submucosa with eosinophils, leucocytes, edema; hypertrophy of muscle and diminution of lumina. Infolding of the epithelial layer is thought to indicate musuular spasm.

16. The eosinophils in asthma undergo a very definite change. They are apparently withdrawn from the blood during the attack and stay in the tissues.

17. Although the right heart is supposed to show organic and electrocardiographic changes in asthma, apparently it is not common in true simple asthma but is seen secondary to infectious "mechanical" changes in the lungs. Incidence varies with different observers.

18. Asthma may occur at any age. It is rather common in young subjects. Sexes are equally represented except in the younger groups (males predominate?).

19. Positive "allergic" family histories have been obtained in 47% of reported cases.

20. The commonest mode of onset is spontaneous (42%), respiratory infection (35%). Skin tests may or may not be positive.

21. Three types of asthma are recognized: Intrinsic, extrinsic, or mixed. Reflex asthma is usually included under intrinsic form.

22. In the literature, response to treatment of lesions of the nose and throat shows marked variation.

23. Sudden death in asthma may occur when "break" in compensation occurs: i.e., when the rising CO_2, buffer interaction in the blood goes beyond 9.5% (normal limit 7.2%). Asphyxia which follows is due to the failure of the respiratory center to

respond to increased blood CO_2.

24. Both of our cases are examples of true asthma with upper respiratory infection (reflex?) and sudden deaths. In one case, exitus was rather prolonged, the other short. Both are due to respiratory center failure (?). They did not show obliteration of the bronchi.

25. In the last case, the meningioma will always be considered a possible contributory lethal factor. The case of the woman, who suddenly died on the operating table is still fresh in our minds. She had a silent brain tumor. Note: Headache in our case after operation (?). In spite of this, the lung findings are those of asthma and the clinical picture typical asthma.

References:

Rackemann, F. M.: Textbook "Clinical Allergy", MacMillan, N.Y. 1931.

Knott, F. H.; Oriel, G. H.; Witts, L.J.; "Report of the Asthma Clinic 1928-30"; Guy's Hosp. Rep. 80:421-430, (Oct.) '30.

Symposium "Asthma": Practitioner 123: 1-96, (July) 1929. (13 authors).

Huber, H. L.; Koessler, K. K.; "The Pathology of Bronchial Asthma"; Arch. Int. Med. 30:689-760 (Dec.) '22.

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II. BARRAGE CONTINUES

May 4 - 6, 1932. Iowa State Medical Society, Eighty-first Annual Session, Sioux City, Iowa.

Pulmonary Arteriosclerosis: A New Clinical Tripod - Henry L. Ulrich.

Present Day Knowledge of All Formation and Pathology - Hal Downey.

Diagnosis of Childhood Tuberculosis - C. A. Stewart.

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May 9, 1932. American Radium Society, New Orleans, Louisiana.

Treatment and Results in Carcinoma of the Lip. Report of 130 cases - O. H. Wangensteen and O. Samuel Randall.

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May 9, 1932. American Association for the Study of Rheumatism, New Orleans.

Treatment of Arthritis. - Macnider Wetherby.

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May 26, 27 and 28, 1932. American Pediatric Society, Forty-fourth Annual Meeting. Plummer Hall, Mayo Clinic, Rochester, Minnesota.

A Comparative Study of the Inorganic Metabolism in Nephrosis and in Edema of Undetermined Origin - Irvine McQuarrie, Louise Frary and Willis H. Thompson.

Note: E. J. Huenekins, Irvine McQuarrie, W. R. Ramsey, F. C. Rodda, Max Seham, Rood Taylor and former F. W. Schlutz ofthe Faculty of the Medical School are members of this organization. As the membership is limited to 100, Minnesota is very well represented.

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June 1 and 2, 1932. The North Dakota State Medical Association, Forty-fifth Annual Session, Grand Forks.

Surgical Clinic - O. H. Wangensteen.

The Recognition and Treatment of Pulmonary Suppuration (Paper) - O. H. Wangensteen.

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June 7, 8 and 9, 1932. American Neurological Association, Atlantic City.

Muscle Action Currents during Mechanical Movements of Muscle Tonus - J. C. McKinley.

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June 20, 21 and 22, 1932. The South Dakota State Medical Association, Fifty-first Annual Session, Watertown.

X-ray Diagnostic Clinic - Leo G. Rigler.

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(To be continued)

III. Medical Fellow, Johannes K. "Joe" Moen, leaves for Rockefeller Institute, August 1, 1932. Honor Graduate, South High School, Minneapolis, he took his pre-medical

and medical work at Minnesota. Degrees: B.S., '25; M.B., '27; M.D., '28. Internship, Minneapolis General Hospital '28; Housemanship, Eitel Hospital '29; private practice 1 year; came to University Hospitals as Medical Fellow Feb. '30. A.O.A. and Phi Rho Sigma. Research: Quinine and derivatives compared with specific immune sera in experimental pneumococcal infections: Immune reactions in diabetics (see Bulletin III, No. 29, 373, (Apr. 21), '32; Blood protein changes in relation to sedimentation in pneumonia, experimental infections and artificial fever. In New York, he will be associated with Homer Swift in the investigation of rheumatic fever infections.

Quiet, modest, efficient, few young men in our group have done their job so consistently well. Has won increasing acclaim for his clinical ability and has shown a decided flare for investigation. He has justified every prediction made of him since his high school days. He leaves with best wishes of all for success in his new connection. We like you, Joe -- are going to miss you -- know you are going to make good and do your bit in spreading the fame and good name of Minnesota.

P.S. Look him up, will you, Hy?

IV. We thought when we moved to M3 that we would have plenty of room for all who cared to come to Staff Meeting. Last week, we reached a new high (120) and they are out in the corridor again. Before we got under way, Dr. Carlson asked if we removed the dishes before we started our discussions. The idea is not bad (none were thrown), although there was plenty of static. Among other things, we learned that:

The innervation of the colon is still a matter of conjecture, but it is the parasympathetic. Anyone who can show a gradient in the large bowel is a better man than I am. Distension of the gut of an intact animal (sensory nerves), reproduces all the signs of bowel obstruction - the best treatment of the type of patient under discussion is "relaxation." Jacobson, Chicago (one of my students), I am glad to learn how you do things in this Clinic (now what did he mean?).

Surgeons and internists should keep away from our patient and her kind; a good psychiatrist is the man - under sedatives and a hot bath, the signs of bowel obstruction will disappear - the spasm is due to autonomic imbalance (they are stealing your stuff, Henry). The type is well-known - characteristic facies, long chest, drop heart, surgical scars, probably psychogenic (see page 405, top of left column).

The blood chemistry changes in bowel obstruction are due to hypotension renal insufficiency (retention of metabolites), the chlorides are all important, may be vomited out or collect in distended gut (smoke your pipe and wait) which was promptly denied because of absence of such findings in low obstruction. Distension is an important factor (see III, No. 29, 372 (Apr.21) 1932. Louis Sperling). Priority is claimed in our Department of Surgery for decompression in simple intestinal obstruction. Last seven cases of simple mechanical obstruction successfully relieved in this way. We are indebted to our guest of honor, Internist George E. Fahr, and Surgeon Owen H. Wangensteen for very lively discussions.

V. Hospital Day:

This is Nurse Florence Nightingale's birthday and all are invited to visit "your hospital". Nurses will be graduated, radio talks given, babies brought back to visit, tea poured, flowers donated, visitors escorted through. The idea originated in the brain of Matthew O. Foley, Editor-Hospital Management, Chicago; has now spread around the world. The public is asked to select some hospital as their own (as they would a physician), to come and learn first hand of the advantages of being cared for in one of our institutions when ill. There will be open house at the University Hospitals - we are helping by a radio talk, a graduating address for Abbott Hospital, an evening program at St. Mary's Hospital, good advice to the mothers of babies born at Fairview Hospital during the past year, and a High School Assembly in St. Paul. All are asked to work just a little harder - give a little better service to the people of this state for faith and confidence in this institution.

VI. Footnotes:

No. 1. Lung sections show marked emphysema. In some places the bronchi

do not show any special changes; in others they are dilated, the epithelium is flattened, the walls (of muscle) are greatly thickened (mucin in some). There is no bronchitis, no pnuemonia. A few arteries show thickening of wall. No constricted bronchi or infolding of epithelium seen. The dilated bronchi are a surprice!

No. 2. The lung shows exactly the same change (except for blood vessels - no thickening). The severe emphysema is the same - no mucin or bronchitis. In addition a few fibrous scars and thickened pleura are present. No evidence of active tuberculosis. Does it mean the constricted bronchi are way down near atria to alveoli? The epithelium of related bronchi is so flat it appears atrophic.

Brain sections (dura) show typical benign, extremely calcified dural fibroma or meningioma or psamoma (all the same). A small yellow tumor in ovary is benign fibroma with fat?

No. 3. What is cardiac asthma? We made the rounds and learned that it was:

a. Paroxysmal dyspnoea associated with acute left-ventricular failure (usually temporary) seen in any disease involving left heart.

b. Association of 2 in same person - no relation in many instances.

c. A true lung-heart-spastic combination intimately related.

Note: More voted for first type as most frequent.