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of

BRONCHIAL ASTHMA

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The secondary pathological changes which result from bronchial asthma have long been minimized because it has been considered to be primarily a disease which affects the respiratory system. However, the more one carefully considers sufferers from bronchial asthma, the more inclined is one to realize that, not only is the respiratory system involved, but also the cardiovascular system, and that, frequently to a degree which requires our immediate attention.

Literature research on the effect of bronchial asthma on the cardiac system has proven to be a debatable question. Much confusion has resulted from the use of the term "asthma" to denote any paroxysm of shortness of breath, but defined by Coca (6) "bronchial asthma is a symptom complex characterized by a form of recurrent attacks of paroxysmal dyspnea with a prolonged expiratory phase and an associated wheezing, coughing, and feeling of constriction in the chest, which is generally believed to be a manifestation of allergy."

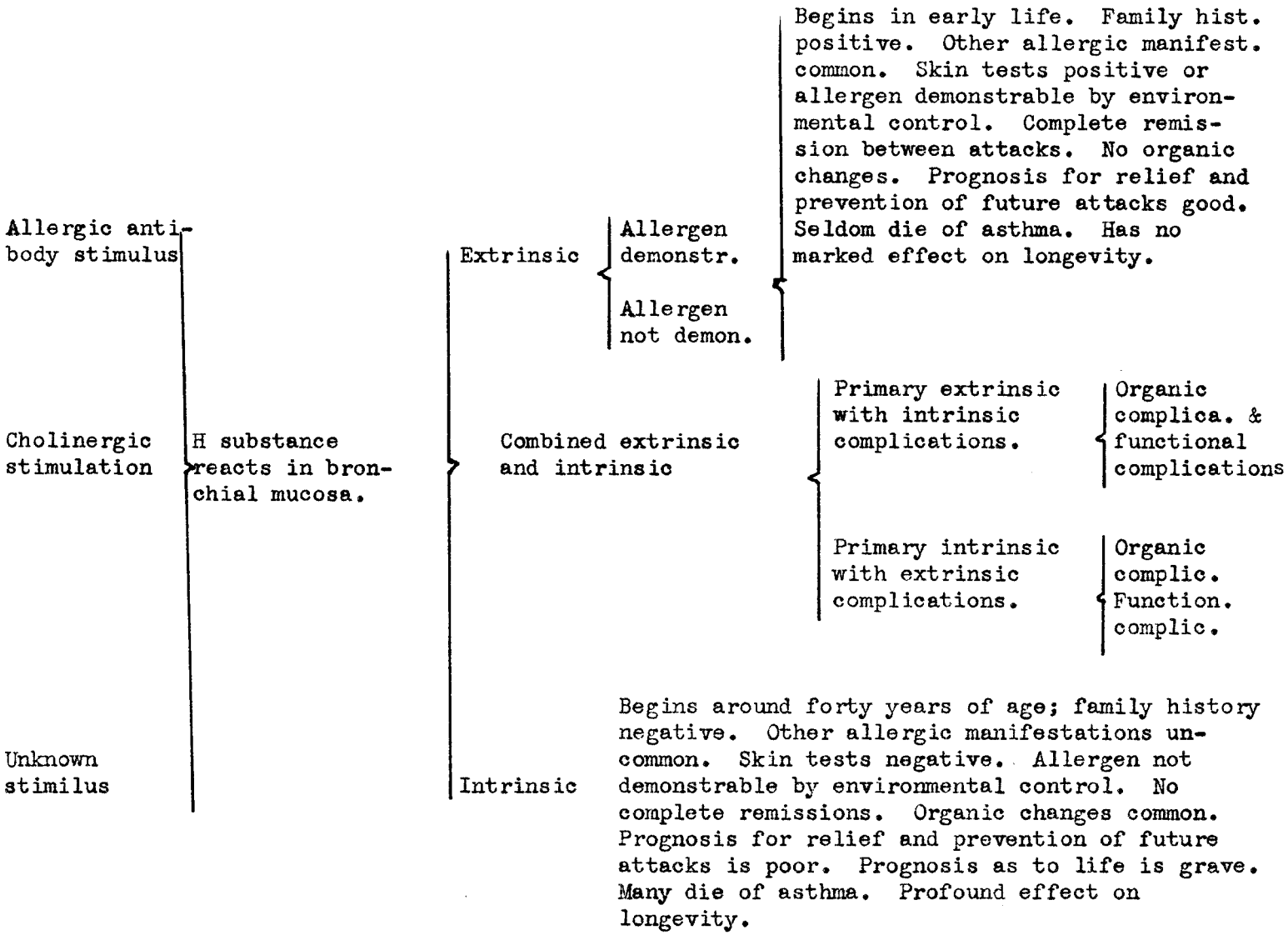
I shall endeavor in this paper to review the effects which bronchial asthma has upon the cardio-vascular system and attempt to show the importance of early diagnosis and treatment in order to minimize the secondary cardiac changes which will result in the majority of cases of long standing

bronchial asthma. The above statement, however, is in accordance with the literature which shows that the reports on alteration of the heart and of the circulation in bronchial asthma are not uniform. In order that the proper evaluation of cardio-vascular pathological changes may be made, I shall consider all phases which tend to give this diversified opinion; this will include clinical material, electrocardiographic studies, roentgenological changes, experimental studies and post mortem findings with their critical interpretation.

In order to have a clearer understanding of bronchial asthma it is necessary to have in mind a workable classification which will adapt itself to any form of asthma. It will be evident that the terms "cardiac asthma" and "renal asthma" are rightfully excluded, because they are terms descriptive of the underlying cause in a few cases. However, as shown by Harkavy (19) diseases of the heart and arteries may coexist with asthma, the casue of which may be entirely separate and independent.

The following classification is by:

Cohen, Milton B. (7) M. D. F.A.C.P.


Allergic antibody stimulus
Cholinergic stimulation
H substance reacts in bronchial mucosa.
Unknown stimilus
Extrinsic
Allergen demonstr.
Allergen not demon.
Begins in early life. Family hist. positive. Other allergic manifest. common. Skin tests positive or allergen demonstrable by environmental control. Complete remission between attacks. No organic changes. Prognosis for relief and prevention of future attacks good. Seldom die of asthma. Has no marked effect on longevity.
Combined extrinsic and intrinsic
Primary extrinsic with intrinsic complications.
Organic complica. & functional complications
Primary intrinsic with extrinsic complications.
Organic complic. Function. complic.
Intrinsic
Begins around forty years of age; family history negative. Other allergic manifestations uncommon. Skin tests negative. Allergen not demonstrable by environmental control. No complete remissions. Organic changes common. Prognosis for relief and prevention of future attacks is poor. Prognosis as to life is grave. Many die of asthma. Profound effect on longevity.

Assuming from the foregoing classification that the etiological factors are manifold in the production of bronchial asthma, I shall proceed to the physiological changes which occur in the lung and questionably produce secondary cardiac changes. Before one can consider the cardiac changes it is essential to understand the physiological changes in the lung which will tend to reflect its effect on the heart.

Bronchial asthma is a paroxysmal disease in which acute oxygen want is caused by a spasm of the smooth muscles of the finer bronchioles. Difficulty is experienced both in inspiration and expiration but, because there is a natural tendency for the bronchioles to narrow during expiration and dilate during inspiration, the greatest respiratory effort is exerted during expiration. The expiratory muscles compress the chest and the abdominal muscles contract in the attempt to squeeze the air from the lungs. The intra-pulmonary pressure is greatly elevated and the air escapes through the constricted tubes with a distinct wheezing sound. Owing to this difficulty and prolongation of the expiratory phase, normal deflation of the lungs cannot occur before the next inspiration ensues. The lungs, therefore, remain almost maximally expanded even at the end of expiration, hence during the asthmatic paroxysm a very large volume of residual air is present in the lungs. Thus it is seen that lungs in emphysema are in a state of

extreme distension as a result of the enlargement of the air sacs. The latter, however, show fewer alveoli in their walls owing to the atrophy of the inter-alverolar septa. Contiguous air sacs within a lobule coalesce or even adjacent lobules may fuse to form large air spaces. For this reason the total respiratory surface is reduced. The alveolar and capillary walls become thickened and the interstitial pulmonary tissue increased. Many capillaries become occluded. The pulmonary elastic tissue is reduced in amount so that the lungs, when removed from the thorax, do not collapse normally but remain in an overexpanded state (4). The aforementioned factors which effect the pulmonary system as a result of long standing bronchial asthma have formed the basic principles for this somewhat controversial issue. Do cardiac changes result from the pulmonary pathological changes?

It has long been recognized that a mechanical relationship exists between the pulmonary circulation and the condition of the right side of the heart. Clinically, it is known that prolonged pulmonary stasis and increased pressure in the pulmonary circulation result in right heart enlargement. In mitral stenosis or where pulmonary resistance increases, the initial tension of the right ventricle increases with the pressure in the pulmonary vessels; hypertrophy then follows.

The impression has generally prevailed that there is hypertrophy and dilatation of the right heart in bronchial asthma. The assumption according to W. D. Paul (33) is that as a result, first of increased pressure in the pulmonary circulation during a paroxysm of asthma, and secondly, injury to the pulmonary capillaries by the emphysema, the right heart will sooner or later manifest the usual signs of overactivity, namely, hypertrophy and dilation.

However, the subject under discussion has long been one of extensive controversy. In 1920 two of the great American systems of medicine were published; in one Walker (44) writes, "Although the elasticity of the lung in an asthmatic after a time becomes impaired and thus makes the prognosis more unfavorable, the integrity of the myocardium is rarely weakened." In the other, Miller (31) asserts that, "as the result of repeated heart strain associated with the attack and the cardiac changes attending on chronic emphysema, evidence of cardiac decompensation is very apt to appear early. The appearance later in life of cardiac decompensation should serve as a warning that bronchial asthma is to be taken seriously and every effort made to prevent a recurrence of the attacks." Most writers maintain that in chronic bronchial asthma followed by emphysema, hypertrophy and dilatation of the right ventricle ensues.

A basic point that must be kept in mind is that a consideration of the effect on the heart of long standing bronchial

asthma becomes essentially a study of the heart in emphysema, for this complication is an organic defect and is almost an inevitable complication of such asthma. Kahn (23) states emphatically that emphysema accompanies long-standing asthma. With that, of course he adds, "pathologically there is marked thinning of the vesicular walls and consequent narrowing of the vessels and capillaries. Occasionally, these become occluded and even torn through. This series of events tends to occur in most cases of bronchial asthma in the long standing and intractable cases more than in those of short duration. The capillary field is thus lessened without the possibility of a compensatory dilatation." He concludes, "that as a result, there is dilatation and atherosclerosis of the pulmonary artery and dilatation and hypertrophy of the right ventricle, as it is called upon to force the same amount of blood as before through the narrowed capillary field of the entire lung and may continue to the point of cardiac insufficiency."

It is believed by Alexander, Luten, and Kountz (1) that possibly the distended lungs in emphysema and the forced expiration induce increased intrathoracic pressure. This, according to the Valsalva experiment, tends to decrease the size of the heart. It is interesting to find that Gotzl and Kienbock (17) in 1908 observed just this reaction in two cases of asthma radioscopically and noted that the hearts were small. Between attacks, they observed that if either of these patients took a breath and

strained with the glottis closed, the hearts were actually seen to diminish in size, whereas the intrathoracic pressure was increased. They actually measured the heart shadows and noted a diminution of the transverse orthoscopic shadow from 8.5 to 6.3 cm. However, it has been found in the present study that when this procedure is carried out on normal persons, the transverse cardiac diameter likewise becomes less.

The above physiological diminution in size has been explained by Alexander, Luten and Kountz as follows: They assumed that during normal inspiration, the negative pressure in the chest increases. This increase in the negativity of the intrathoracic pressure during inspiration is a factor which aids in filling the right heart. During a paroxysm of asthma, intrathoracic pressure does not decrease as it should with inspiration and so the right heart does not fill completely. This, naturally, causes an increase in the venous pressure as shown by the greatly swollen veins of the neck and arms. The amount of blood flowing into the left ventricle decreases and as a result, less blood reaches the systemic circulation. The pressure gradient between extra thoracic veins and right auricle during a bronchospasm is less, causing a reduction in the amount of blood in the right ventricle and therefore, a small, rather than dilated, right ventricle occurs. A subsequent review of cases will show that this theory is not fully substantiated by further investigators in this field.

Geizel (15) explained that the generalized ventricular hypertrophy of emphysema was due to increased abdominal pressure caused by the forced descent of the diaphragm. A resistance to a large part of the peripheral blood flow would thereby be offered and the heart would respond by more forceful contraction of the left ventricle. He believed that the elevated intra-abdominal pressure likewise would hasten the return flow of venous blood through the inferior vena cava to the right heart, whose intake would thus no longer be regulated by the intra-pleural pressure. Geizel concluded, therefore, that both chambers of the heart would be at a disadvantage in emphysema and hypertrophy of each would occur.

However, this theory which Geizel has postulated to account for the cardiac enlargement has been contradicted by experiments which have shown that when emphysema is sufficiently advanced to produce symptoms, there is probably a diminution rather than an increase in the amount of blood in the right auricle. It has been suggested that as the diaphragm descends with the enlarging lungs, the intrapleural pressure becomes more negative and the blood flow to the right heart increased. Overloading may take place at this time. Once the diaphragm is pushed down to its position to contraction and the excursion of the thorax limited by its barrel-ing, the intrapleural pressure promptly rises, and the blood flow into the thorax becomes impeded. Following this, the next factor of obstruction to the flow of blood from the right to the left

side of the heart is brought about by diminution of the capillary bed in emphysema and may contribute to the right ventricular dilatation. This usually occurs in cases of long standing bronchial asthma.

Kretz (26) studied the effect of emphysema, experimentally, on the right heart of dogs. He found it difficult to obtain true values of vascular pressures within the closed thorzx because of the ever changing intrathoracic pressure which is distributed evenly upon all the thoracic structures. He concluded, therefore, that sufficient evidence had not been presented to warrant the assumption that emphysema alone caused hypertrophy of the right heart. From the clinical standpoint, dyspnea, cyanosis, lowered venous pressure are all cardinal signs of both extensive emphysema and of cardiac failure. The emphysema it is believed, is the result of the anoxemia that is due directly to faulty O_2 exchange between the inspired air and the blood. It must be kept in mind that the manner by which the emphysema was produced in this experiment may have a profound effect upon the results obtained because the experimentally produced emphysema cannot simulate that which is found in persons with long standing cases of bronchial asthma. They are basically two different principles and the cardiac manifestations may likewise parallel the manner by which pulmonary changes are produced, hence little respect can be paid to this experimental finding.

With reference to the clinical aspect of the effect of bronchial asthma on the myocardium, it is also evident that for many years there has been a controversy over this issue. Much has been written on this subject, some claiming that the heart is not damaged even in long-standing asthma; others say the heart does become affected. The literature shows that the reports on alterations of the heart and of the circulation in emphysema and bronchial asthma are not uniform.

The literature dates back to 1839 when Andral (2) announced that, "Asthma is a brevet of long life," and this view holds with many to this day. On the other hand clinical evidence can be brought forth to substantiate the viewpoint that the heart is damaged in bronchial asthma. Bishop and Nelson (5) assert that, "the chronic asthmatic has a large distended heart, particularly involving the right ventricle, the heart sounds are weak, and frequently tachycardia is present. The myocardium itself is at fault and, therefore, valvular murmurs are not common. The electrocardiogram usually shows a right predominance and low voltage."

The variety of clinical manifestations are numerous and some reports show an especial frequency of increased blood pressure in bronchial asthma and of arteriosclerosis in emphysema, while others reported a special frequency of conditions of hypotonia. Some are inclined to assume an injury to the entire heart as the

sequence of attacks of asthma; still others (3) are of the opinion that the intrapulmonary increase of pressure means a marked increased labor of the right heart. They also contend that the excessive labor of the right heart, which is rightly assumed in emphysema, must be attributed to the limitation of the pulmonary circulation, but there exists at present no proper and easily applicable method to measure the pressure in the lesser circulation during life.

The occurrence in bronchial asthma of excessive fluctuations of the systemic systolic blood pressure, synchronous with the respiratory cycle, has been noted in the past by a number of observers. Osgood and Ehret (32) have reported on a number of asthmatic patients under various circumstances and the conclusions which were agreed upon closely paralleled those of Tinel and Jacquelin (39).

1. During the asthmatic paroxysm there is constantly present an increase above normal in the respiratory fluctuation of the systolic blood pressure.
2. The amplitude of this fluctuation parallels closely the severity of the asthmatic dyspnea.
3. When the asthmatic paroxysm has ended, the respiratory systolic fluctuation returns to normal limits. An exception of the third statement has been noted. In certain chronic asthmatic patients in whom irreversible

changes have taken place in the lungs, there may be present at times a moderate increase in the respiratory systolic fluctuation, even though the patient appears to be in little or no distress.

Further observations disclosed that the systolic blood pressure uniformly reaches the highest point during expiration and falls to its lowest point during inspiration, both during the paroxysm and during the asthma-free state. Certain experiments with respiratory obstruction in anesthetized cats and in healthy young men which Osgood has reported, showed a similar increase in the respiratory systolic fluctuation with increasing obstruction. The timing of the high and low points of the fluctuation in the respiratory cycle was also the same in these experiments as in bronchial asthma.

The evaluation of this increase can best be estimated by reviewing the clinical material and determine whether or not it increases cardiac efforts. However, before investigating the pathological changes which may take place in the myocardium, I should first like to present the electrocardiographic changes which occur during the course of asthma.

Electocardiographic changes.

A brief explanation of the normal physiology and mechanics of electrocardiographic tracings with their interpretation is presented by Kahn (22) as follows:

The normal Q-R-S group is produced by the algebraic summation of the left ventricular electrocardiogram (levocardiogram) and the right ventricular electrocardiogram (Dextrocardiogram). In the normal electrocardiogram, the effects of the two ventricles, in spite of the greater mass of the left, are fairly well balanced, producing the normal Q-R-S curve. A relative increase in the mass of the one or the other chamber alters the balance between right and left ventricular effects.

When the heart is greatly hypertrophied, preponderance of one side or the other is the main factor influencing the ventricular complex of the eletrocardiogram. Variations in the position of the heart is another important factor. It has been shown that the relative dilatation of the two chambers, on the contrary, plays no appreciable part in determining the form of the ventricular complex. Prominent Q_3 and S_1 in the electrocardiogram are right ventricular effects. R_3 is chiefly a right ventricular effect. The tall R_3 and deep S_1 of right ventricular hypertrophy are the expression of preponderance of the dextrocardiogram.

The following is a discussion of the probable causes of electrocardiographic changes by Harkavy and Romanoff (20) other than pathological changes which must be kept in mind when interpreting electrocardiographic tracing on asthmatic patients.

Anoxemia: Induced anoxemia in both experimental animals and

man has resulted in prolongation of the P-R interval, alterations of the RS-T segment, and T-wave changes. It has been shown that normal persons begin to show electrocardiographic changes at a stage when signs of disturbances of consciousness present themselves. Levy, Barach and Bruenn (27) in a study of oxygen want in cases with cardiac pain, investigated one subject with a normal heart and noted slight flattening of the T waves in Leads 1 and 11 and less deeply inverted T wave in Lead 1V, after the inhalation of a twelve percent oxygen mixture for twenty minutes. There was no effect on the R-T and S-T segments. The arterial oxygen saturation in this subject at the end of the experiment was 67.8 percent. It would seem from such observation that in persons with normal hearts the oxygen want must be fairly severe before electrocardiographic changes begin to appear. Meakins and Davies (29) found that, in certain types of asthma, accompanied by bronchitis, emphysema and marked cyanosis, there was a varying degree of oxygen desaturation. There was no record of any electrocardiographic abnormalities in the cases which they studied, and they concluded that the lowering of the arterial blood oxygen is directly proportional to the chronicity of the lesion and the extent of the emphysema and bronchitis.

Positional Changes of the Heart: Master (28) and other investigators have reported low QRS waves in Lead 1 and right axis deviation in normal subjects with low diaphragms and mesially

placed hearts. He believes that the numerous illusions in the literature as to a tendency toward right axis deviation in bronchial asthma may be attributed to positional changes as a result of a shift of the electrical axis toward the vertical plane. This, nevertheless does not exclude the possible occurrence of right ventricular hypertrophy in cases of long-standing bronchial asthma, with frank right axis deviation in the electrocardiogram.

Epinephrine: Electrocardiographic changes after the administration of epinephrine have been attributed by Wiggers (43) to anoxemia of the myocardium resulting from constriction of the coronary vessels. The injection of epinephrine, however, is not always followed by constriction of the coronary vessels. According to Gollwitzer-Meir and Kruger (16) epinephrine causes coronary dilatation.

In view of the fact that the effects of epinephrine injections on the electrocardiogram are transitory, and the records in our cases were often made during intervals when the patients were relatively confortable, several hours after they had received epinephrine, it is questionable whether this drug had anything to do with the Electrocardiographic changes which were noted.

Cardiac Reactions Following Sensitization:

Numerous investigators (20) have reported that electrocardiographic abnormalities occur in experimental animals during anaphylactic shock. These changes consisted of disturbances of conduction and

abnormalities in the origin and spread of the electrical impulses. They have been attributed by some observers to anoxemia of the myocardium and by others, to toxic substances elaborated during the shock. Concerning the experimental and pathologic observations, the question arises whether the electrocardiographic abnormalities in certain cases of bronchial asthma may not represent allergic responses in the pulmonary and coronary vessels to the agents implicated in the production of the asthmatic seizures. Since, in the cases studied (referred to later) neither epinephrine nor positional changes of the heart could be regarded as responsible for the electrocardiographic abnormalities, the problem becomes one of the relative roles of allergic reactions in the lungs and heart and associated anoxemia.

THE ROLE OF ALLERGIC RESPONSES:

According to the currently accepted theory of the mechanism involved in the allergic response, which implies the liberation of certain injurious agents of a histamine-like character on or within the tissue cells consequent upon antigen-antibody interaction, may be utilized in explaining the phenomena observed.

If the contention is accepted that the effect of histamine products is one of constriction of arterioles and dilatation of capillaries, associated with increased permeability, it is conceivable that, with the elaboration of similar substances

during asthmatic attacks, spasm of the pulmonary arterioles, as well as increased dilatation and permeability of the inter-alveolar capillaries, may ensue. To this may be added contraction of the bronchi which is another effect of histamine. If the constriction of the vessels is sufficiently marked it may interfere with the pulmonary circulation, and the tissue edema which results from the increased vascular permeability may act as a tamponade, and add to the burden of the pulmonary flow. The resulting obstruction to the circulation in the lung could give rise to hypertension of the lesser circulation. Such an increase of tension would augment the load of the right ventricle, and when transmitted to the right auricle, would be reflected in the electrocardiogram by increased voltage of the P waves.

In the ventricular changes it is well known that aberrations of the QRS complex and RS-T segments as well as T-wave changes, may result from pericardial involvement, myocardial damage brought about by local anoxemia consequent upon coronary artery constriction, such as in associated with coronary occlusion, or the direct toxic effects upon the myocardium of various systemic diseases. Since the ventricular electrocardiographic changes in many cases showed a direct temporal relationship to the occurrence and subsidence of both the asthmatic attacks and pulmonary infiltration, they may also be

considered as manifestations of various degrees of allergic response of the vessels of the heart, with resultant coronary insufficiency and myocardial ischemia. It will be noted that this view is parallel to the theoretical explanation given above in respect to the allergic reaction.

The above mentioned factors must be borne in mind when reviewing the following reports on patients with bronchial asthma and the corresponding electrocardiographic changes. The external factors mentioned may also explain the cases in which the electrocardiograms showed right ventricular enlargement but was not confirmed at autopsy. Consideration must also be given to false interpretations in which extrinsic cardiac factors were not considered in many of the reports of electrocardiographic changes in patients with bronchial asthma.

Harkavy and Romanoff (20) had fifty patients with bronchial asthma in their investigation upon which electrocardiograms were taken. Of this group, twenty of them presented electrocardiographic changes, exclusive of sinus tachycardia. The most prominent changes recorded were: 1. Prominent P waves, 2. QRS disturbances, 3. RS-T transition changes, and 4. T wave alteration.

The hearts of these patients were negative on ausculation, but tachycardia, ranging between one hundred and one hundred thirty beats per minute occurred during asthmatic attacks. The electrocardiographic abnormalities consisted of high P waves alone in

six cases, and high P waves with QRS and T-wave deviations in nine others. In the remaining five cases the alterations were confined to the QRS and R waves only.

In nine of the twenty cases the electrocardiographic abnormalities disappeared with the termination of the asthmatic paroxysm, whereas in five cases the changes persisted. One of the five patients with irreversible changes showed persistent enlargement of the P waves only. This man had had asthma for thirteen years, together with pulmonary emphysema and a lung cyst. The other four patients presented changes in the P, QRS, and T waves.

They (20) interpreted the foregoing results as follows: There was no clinical indication or laboratory evidence from the study of the oxygen saturation of the blood in three cases that respiratory anoxemia was the primary factor in inducing the electrocardiographic changes that were observed. Moreover, the relative unimportance of respiratory anoxemia was also illustrated by the fact that three cases showed that electrocardiographic abnormalities persisted during asthma-free periods, when hyperergic manifestations were developing in other shock tissues.

The auricular and ventricular complexes may be explained on the basis of coronary insufficiency, brought about through compression of the right coronary artery because of a rise in interventricular pressure consequent upon an increase in tension in the lesser circulation. The latter may be considered the

result of allergic vascular reaction in the lung. Such a mechanism could account for the high P waves, as well as changes in the QRS and T waves.

On the opposing side there was a series of electrocardiographic reports on seventy-five patients seen at the Allergy Clinic of the State University of Iowa Hospital with bronchial asthma (33). Of this group there was only one which presented cardiac hypertrophy. This patient had a hypertension and the clinical diagnosis was that of arteriosclerotic heart disease. Electrocardiograms were taken in ten of the patients. The mechanism was normal in nine, and the other had a rhythmic bigeminy. In one instance a left axis deviation was noted, but no right axis deviation was found. No changes in T-waves or Q waves suggestive of coronary artery disease were encountered.

How much reliance can be placed on this survey is questionable because the duration of bronchial asthma and the age of the patient is definitely a factor to consider when attempting to evaluate the effect bronchial asthma has on the heart.

However, in support of the previous study just mentioned is the work of Creip (11) who also reviewed the data in fifty cases of true bronchial asthma. He found that during a paroxysm of asthma the electrocardiograph revealed a delay in the auricular ventricular conduction. This is as expected since asphyxia usually gives such a conduction defect. In this series twenty-one curves were normal, fifteen showed sinus arrhythmia, ten

left axis deviation and four right axis deviation were found who had definite mitral disease.

He concluded from his studies that bronchial asthma has no permanent damaging effect on the cardiovascular system.

In contrast to Creip's work, is that of Colton and Ziskin (9) in which they made a study of the clinical findings in eighty-four cases of bronchial asthma.

Electrocardiograms were made on fifty-six of the eighty-four cases. Thirty-four (or sixty-one percent) were found to be entirely normal. Eleven or twenty percent showed definite evidence of myocardial involvement. Three of these, however, could be accounted for on the basis of organic cardiac disease. The electrocardiographic findings in these eleven cases were as follows: Delayed auriculo-ventricular conduction, two; arborization block, one; and negative T-waves, eight. The T-wave inversion was present in lead 11 and lead 111, this being indicative of right heart involvement.

An index of preponderance was used $(R_1 \neq S_3) - (S_1 \neq R_3)$ as a further study to correlate the changes with the duration of asthma. It was found that in the group with asthma of less than one year duration the index was -3.3; in the group with duration of two to ten years the index was -5.2; while in the group with a duration of over ten years the index of preponderance was -6. It is evident, therefore, that the tendency to right axis deviation increased as the duration of the asthma increased.

The fact that right ventricular preponderance was observed in twenty percent of the cases and that the index of preponderance showed a definite tendency to right-axis deviation in the entire group, also that this tendency increased as the duration of the asthma increased, would indicate that asthma causes a definite strain on the right heart.

These authors (9) conclude that the heart does not remain singularly free from injury in bronchial asthma, and that right ventricular strain with a tendency to myocardial involvement and heart muscle damage does occur.

This conclusion is further substantiated by Schiller, Colmes, and Davis (38) who made a clinical study of fifty-four patients with bronchial asthma to determine the incidence of cardiac abnormalities of this origin.

Electrocardiograms were available in forty-six of these cases. Fifteen (thirty-three percent) of these were within normal limits. Thirty-one patients (sixty-seven percent) showed the following abnormalities: prolongation of the QRS interval, three cases; inverted T waves in Leads 1 and 2, seven cases; abnormalities in Lead 4, three cases; an abnormally deep Q wave in Lead 3, two cases; a deep S wave in Lead 2, seven cases; and auricular fibrillation, one case. Thirteen patients (twenty-eight percent) showed left-axis and six (thirteen percent) right-axis deviation. A tendency to right-axis deviation was further noted in four other patients (nine percent).

These findings of electrocardiographic changes and associated findings of cardiac pathology at autopsy, has lead these investigators to believe that cor pulmonale due to chronic bronchial asthma is a more common disorder than is generally recognized.

Forthwith is presented excerpts from publications of Kahn (23) who made a very careful investigation of fifty cases with a detailed analysis of the electrocariographic records.

Four predominating characteristics were found in the analysis of the electrocardiograms of these cases: (1) left ventricular preponderance; (2) right ventricular preponderance; (3) high P (auricular) wave in Leads 11 and 111; (4) T wave inverted in Lead 111. The table below will show the rather common association of high diastolic blood pressure and left ventricular preponderance.

Table 1 - Classification of electrocardiographic changes according to diastolic blood pressure.

Diastolic blood-press.	No.cases	No prepon-derance		R.V.P.		L.V.P.		T3 inverted	
		No.	%	No.	%	No.	%	No.	%
Under 70 mm.Hg.	9	4	44	4	44	1	11	2	22
70 to 79 mm.Hg.	14	7	50	2	14	5	35	3	21
80 to 89 mm.Hg.	11	6	54	1	9	4	36	2	18
90 to 99 mm.Hg.	8	1	12	2	25	5	62	2	25
100 and over mm.Hg.	8	1	12	1	12	6	75	1	25
Totals.....	50	19		10		21		10	

In a case of hypertension, therefore, when there is no ventricular preponderance, we may assume the coesistence of right heart hypertrophy. Of the twenty-one cases of left ventricular preponderance, the largest number showed hypertension. It is seen that the higher the diastolic pressure, the greater is the proportion of cases showing left ventricular preponderance. It is observed that in a number of cases, even with high blood pressure, there is no left ventricular preponderance, that is, the normal balance between the musculature of the two ventricles is maintained. This implies and indicates right ventricular hypertrophy. The majority of cases showing left ventricular preponderance are above the age of forty years or with a diastolic pressure above 90 mm. Hg.

The frequent association of the high P wave with right ventricular preponderance suggests that this is another evidence of the effect of pulmonary stasis on the right heart. Since the effect is first upon the ventricle and only secondarily upon the auricles, a high P wave would theoretically not be found in association with left ventricular preponderance except in cases of mitral stenosis. This assumption is supported by the analysis of their tables. It is an unusual finding that the four cases showing a high P wave in Leads II and III occur in cases in which there is right ventricular preponderance.

Thus, it is seen that twenty percent of the fifty cases studied showed electrocardiographic evidence of right ventricular

preponderance. Of the remaining cases approximately fifty percent of these showed left ventricular preponderance and were associated with hypertension; factors which influenced the hypertrophy of the left ventricle to a degree sufficient to mask the electrocardiographic evidence of right ventricular hypertrophy.

This work of Kahn is critized by Unger (41) because:

1. X-Ray examinations were not made.
2. He did not publish criteria by which the diagnosis of bronchial asthma was made.
3. He included cases of high blood pressure, which accounts for many of his left ventricular preponderances. But he adds, that many of Kahn's cases must have been true bronchial asthma and the finding of twenty percent with right ventricular preponderance cannot be thrown aside.

The following and final study on electrocardiographic changes in bronchial asthma was made by Unger (40) who conducted a thorough and careful study of seventy-four cases. The cases were taken in order without any selection, except that all were diagnosed true bronchial asthma. This was accomplished by the usual history, complete physical examination, thorough skin testing, chest x-rays, sputum, blood counts, and Wassermann test.

To offset the argument against Kahn's work all doubtful cases were excluded. All cases of high blood pressure and all with cardiac histories, or who had definite clinical evidence of myocardial degeneration as shown by large hearts with hypertension

and angina pectoris were omitted.

Table 1 below summarizes the findings and groups the cases according to age. The results are as follows:

1. Only twenty-three of seventy-four gave a perfectly normal electrocardiogram.
2. Thirty-five showed a low R in Lead 1 and a high R in Lead 111; this is considered by competent electrocariologists to indicate a tendency toward right axis deviation.
3. Four additional cases gave a frank right axis deviation or right ventricular preponderance.
4. Seven showed left axis deviation, indicating left heart strain.
5. Fourteen cases revealed mild conduction disturbances.

TABLE 1

Age in years	1-9	10-19	20-29	30-39	40-49	50-59	Total	Per cent
Normal	5	4	1	6	3	4	23	31.0
Low R_1, High R_3	7	7	9	8	3	1	35	47.3
R.A.D.	0	1	0	0	1	0	2	2.7
R.V.P.	0	0	1	1	0	0	2	2.7
L.A.D.	1	0	1	1	2	2	7	9.4
Conduction Disturbance	0	2	3	2	5	2	14	18.9
Total Cases	13	14	15	18	14	9	83	---

The conclusion drawn by Unger is that it is evident from this series that there is a definite damage or tendency toward damage to the heart in bronchial asthma. The small percentage of perfectly normal tracings should make us try still harder to see these cases

early, before the complicating emphysema and bronchitis come on and before the heart is damaged.

It has long been a controversial question as to whether bronchial asthma is a contributing factor in the production of heart disease. All previous studies have been made on adults where other disease processes are often concomitant. Derbes and Engelhardt (12) have made a study of asthmatic children in an attempt to determine whether or not bronchial asthma is a predisposing factor to the production of heart disease. A study of seventeen asthmatic children was made, with an average age of nine years and an average duration of bronchial asthma of 4.7 years.

All roentgenological studies were interpreted as normal, however, with the stipulation that errors are possible as a result of postural changes, etc.

Cardiographic studies were done by electrocardiographic methods using three conventional leads, plus precordial leads. All tracings were recorded as normal with no variations in rhythm.

The conclusions drawn were that in children uncomplicated bronchial asthma is not a factor in the production of heart disease.

These same authors (13) made a clinical study of twelve children between the ages of five and fourteen in an effort to determine heart size. Standard methods were employed and the study revealed, with only three exceptions, the actual transverse

diameter is less than the predicted diameter, and in these the difference is minimal. They stated that there is absolutely no certain method of determining heart size ante mortem, however, after applying all available methods they are confident that bronchial asthma is not a factor in heart disease.

Turning to the cardio-pathological changes in adults which have been reported, we see that the number of autopsied cases with bronchial asthma reported in the literature, however, is not large, and not all writers have recorded full data on the heart.

Unger (41) contributes the paucity of autopsy reports in bronchial asthma as due to several factors: (1) the tendency of asthmatics to live for many years after the onset of symptoms; (2) the difficulty in obtaining autopsy permits; (3) the frequent complications which may overshadow the asthma, for example; pneumonia, bronchitis, bronchiectasis or heart disease, especially in older asthmatics.

In reviewing the literature upon this subject, we shall discuss two principle groups, first, those discussing bronchial asthma in relation to cardiac disease or accompanied by it, and secondly, gross post mortem findings and microscopic studies.

Harkavy (19) points out that spasmodic asthma with emphysema might produce right ventricular hypertrophy. He also felt that in chronic cases constant strain on the right heart is certain to bring about right-sided cardiac hypertrophy and

insufficiency, and gives as his opinion that the patient dies essentially of cardiac failure. In discussing the work of Michael and Rowe (30) Harkavy also states that he saw definite eosinophilic infiltration in the walls of the pulmonary arteries, leading to the conclusion that allergic reaction may occur not only in the lung tissue but in the blood vessels themselves, and that the vascular system may be the seat of manifestations due to hypersensitiveness.

However, it is the opinion of the authors (30) that the heart in bronchial asthma is rarely abnormal on general physical examination. They reported on two fatal cases of bronchial asthma. At autopsy, the gross findings in one case were negative, and in the other case there was slight paleness of musculature with consistency less firm than normal. On microscopic examination the musculature of this heart presented a mild degeneration and no evidence of hypertrophy, interstitial fibrosis, fatty degeneration or infiltration. The microscopic examination of the second heart in this report was entirely normal as were the pulmonary vessels.

Fisher, and Beck (14) report one case in which, at autopsy, the heart was found to be moderately hypertrophied and there was some dilatation in the conus area. There were three or four small, firm yellowish-beaded nodules on the mitral valve leaflets. The chorda tendinae were somewhat thickened at the valvular end. The anterior papillary muscle was a little hypertrophied. The cusps

of the aortic valve were slightly thickened, and at the base of each was an atheromatous plaque. The coronary arteries were essentially normal, with the exception of a few atheromatous plaques in the intima. On microscopic examination of this heart, it showed an old endocarditis and hypertrophy of the right ventricle.

Colton and Ziskin (9) reviewed nine cases in which bronchial asthma was the cause of death and six autopsies were performed. One patient that died of asphyxia showed acute right heart dilatation; two with various degrees of emphysema and bronchiectasis. The remaining three showed hypertrophy, dilatation, and congestive failure. The authors concluded that heart involvement does occur in asthma as the disease progresses and emphysema ensues.

In a report of nine hundred twenty-two patients of the Peter Bent Brigham Hospital who had had either a primary or a secondary clinical diagnosis of bronchial asthma of this number twenty-nine died. Ten autopsies were performed on twenty-three of these twenty-nine patients. In seven of these twenty-three patients the clinical picture was that of status asthmaticus, the autopsy observations were consistent with bronchial asthma and no extrapulmonary cause of death was present.

In five of seven cases the heart was entirely normal as far as physical examination was concerned; in the other two cases the

findings were enlargement. In some instances there were signs simulating right-sided heart failure, such as a questionably enlarged liver in one case, distention of the veins of the neck in two cases, dependent edema in three cases.

Post mortem examinations showed that there was no important cardiac lesion in any of these patients. The hearts weighed from 200 to 365 gm., and there was a slight right-sided dilatation in two instances but in none did the musculature of the right ventrical measure over 5 mm. in thickness. Occasionally slight relative hypertrophy of the right side was noted. In no case was there significant valvular coronary arterial disease, and microscopic sections showed no evidence of myocardial scarring.

In accordance with these findings, Rubin (36) made a study of fifty-five cases of asthma with an average duration being fourteen years. Out of this series the actual finding of right ventricular enlargement was present in only a very few cases. There were only five which showed a suspicion, but nothing more, of enlargement of the right ventricle alone. A definite selective or preponderating enlargement of the right ventricle was not found radiologically in a single instance. In those cases in which enlargement of the heart was present, such enlargement was general and shared by both ventricle. There were fourteen such cases and these patients were mostly forty years of age and over, with advanced emphysema. The large majority of cases, including

several cases of well-marked emphysema in younger subjects, showed no cardiac enlargement.

Similar findings have been reported by Podkaminsky (34) who examined the heart radiologically in a number of cases of asthma with emphysema.

Hansen (18) reviews fifteen deaths, seven of which showed right ventricle involvement. He concludes that those with cardiac involvement are usually the ones with excessive secondary lung infection and fibrosis. His question is a pertinent one, as to whether fibrotic obstruction of bronchi and collapse, finally leads to secondary right heart hypertrophy.

Sprague (37) reports two cases of death in an asthmatic attack. One of these showed extreme dilatation of the right ventricle. In the other case, the heart showed right side hypertrophy.

Rackemann (35) describes death in an asthmatic individual with a post mortem finding of emphysema and of a heart which was smaller than normal but which showed marked dilatation of the right ventricle.

More recent studies of the effect of emphysema in bronchial asthma have been conducted by Kountz, Alexander, and Prinzmetal (24). They studied this process both in human beings and experimentally in nineteen dogs that survived the operation.

Under the human studies, seventeen cases came to autopsy and

the cardiac findings were significant. In none were valvular defects present, but in a few, especially older patients, there was some degree of fibrosis in the myocardium. In seven cases the hearts appeared normal, or were distinctly small. In ten cases there was evident enlargement. In these instances a dilatation of the right ventricle was constant, and obvious thickening of the right as well as of the left ventricular wall was noted. The findings were compared with similar observations on twelve normal controls made by Herrmann and Wilson (21) whose method of heart examination was used. In each instance, hearts that appeared normal or enlarged on inspection proved to be so on measurement. The sole relation of the two groups to clinical data was that the average duration of symptoms in the series with hypertrophy was somewhat longer, although there was comparable individual cases in this regard in both groups. They also found that in every instance in which right ventricular dilatation occurred, there was left ventricular hypertrophy. The authors found no reason for the latter obscure finding.

From these observations they conclude that the heart is affected in the majority of patients with emphysema, and that the lesion, cardiac hypertrophy, with dilatation of the right ventricle when advanced, may produce symptoms, but probably has no clinical reflection in its earlier stages.

In the experimental studies on dogs, Kountz, Alexander, and Prinzmetal (24) emphysema was produced by painting the bronchi with

silver nitrate. In order to produce pulmonary distention, large amounts of lung were destroyed, one lobe at a time, and then removed surgically. The duration of emphysema varied from nine months to fifty-two months and the heart appeared essentially normal in eight cases, and eleven were pathological. Of the latter, right ventricular dilatation was prominent in all. The others showed some hypertrophy of the right and left ventricles. They concluded that there is experimental evidence which indicates that the right ventricular dilatation and hypertrophy occur chiefly in the earlier stage of emphysema, when the lungs are in the process of distention.

On the opposing side of cardiac pathology occurring in the early stage of emphysema, is the study made by Waverla (42) at autopsy of a thirty-six year old man with a clinical diagnosis of bronchial asthma, emphysema and right heart hypertrophy. He believed that circulatory stasis in combination with mechanical demands may lead to such changes of the elastic tissue. Occlusion of small branches of the pulmonary artery produced a considerable hypertrophy of the right heart. Calcium was found in the lungs which points to a process of degeneration. Numerous recurrences of asthma probably produced a hypertrophy of elastic fibers and when the limit of elasticity was surpassed, the fibers yielded and tore; incrustation with calcium followed; and chronic venous stasis was a contributing factor. The author considers the study of this case as a contribution to the pulmonary pathology in

bronchial asthma and as a proof that a peculiar form of pulmonary sclerosis may produce a hypertrophy of the right heart.

All microscopic findings in patients with cardiac hypertrophy and dilatation are extremely similar but extremely variable depending upon the duration of the asthma and the cause of death. According to Colton and Ziskin (8) the case in which cardiac pathology was present, it was rather common to find a fibrotic myocardium, and moderate narrowing of the lumen of the coronary artery. Occasionally the myocardium contained a few scattered lymphocytes and polymorphonuclear neutrophic leukocytes and occasional fibroblasts.

In an article by Anthony (3) reference is made to the microscopic studies by Franz. In his series he found the endocardium to be thickened and a snowy white color; the myocardium showed localized foci which contained lymphocytes, young fibroblasts and mature fibroblasts.

In general, it can be said that the microscopic findings closely parallel the duration of asthma and the gross cardiac pathological findings.

Summary: It is quite evident that the reports on alteration of the heart and of the circulation in bronchial asthma are not uniform. After considering all possible phases by which this problem can be studied, it was found that discrepancies exist in the clinical material, electrocardiographic studies, roentgenological changes and post mortem findings.

Much criticism has arisen with respect to the manner of investigation on the work that had previously been carried out in the field of cardiac changes in bronchial asthma. Most authors contend that the pathological findings are directly related to the type and duration of the asthma, and also, the underlying separate disease entities which often coexist with asthma. Hence, the principal point of controversy arose, were the cases studied diagnosed as true uncomplicated bronchial asthma with no superimposed cardiac lesions?

Clinically, it proved difficult to evaluate the cardiac effect of bronchial asthma because of various physiological changes and underlying silent pathological changes. The post mortem findings also were not consistent but a great percentage showed definite evidence of cardiac strain. After this rather extensive review of the literature on this subject, I would be inclined to conclude that in chronic pulmonary emphysema, a gradual transformation of the heart occurs. This transformation being characterized anatomically by a hypertrophy and dilatation of the right side of the heart.

It is clearly illustrated that there is an intimate connection between asthma, emphysema and the heart. It should be considered, above all things, that cases of pulmonary emphysema are not so much sufferers from pulmonary disease as they are from heart disease. No definite conclusion can be drawn but

since a large percentage of the cases with bronchial asthma show cardiac changes, I would deem it advisable to use every precaution and prophylatic measure which would reduce the severity of the asthma.

In the treatment of pulmonary emphysema, particular attention should be paid to the heart and the circulation, physical methods of treatment should be prescribed with the corresponding care. One must avoid too one-sided treatment of the pulmonary process only.

It has been shown with a reasonable amount of consistency that the resulting effects of bronchial asthma indicate that the heart should never be neglected. When the patient first begins to complain of symptoms referable to the cardiac system between asthmatic attacks, immediate cardiac therapy should be instigated. It is not advisable to continue with the remedies to relieve the asthmatic condition, without immediate consideration of the probable myocardial involvement and at the slightest signs of decompensation of the emphysematous heart, prompt cardiac therapy should be instituted.

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