CARDIOVASCULAR DYNAMICS IN

PULMONARY EMPHYSEMA
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By

Alexander Duncan Gillanders

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# CONTENTS

<table>
<thead>
<tr>
<th>CONTENTS</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td><strong>SECTION I</strong></td>
<td></td>
</tr>
<tr>
<td>EMPHYSEMA OF THE LUNGS</td>
<td>6</td>
</tr>
<tr>
<td>Nomenclature</td>
<td>6</td>
</tr>
<tr>
<td>Historical Review</td>
<td>7</td>
</tr>
<tr>
<td>Evolution of modern concept of emphysema</td>
<td>7</td>
</tr>
<tr>
<td>Pre-Laennec literature</td>
<td>13</td>
</tr>
<tr>
<td>Histology of the emphysematous lungs</td>
<td>16</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>17</td>
</tr>
<tr>
<td>Respiratory obstruction</td>
<td>19</td>
</tr>
<tr>
<td>Experimental emphysema</td>
<td>20</td>
</tr>
<tr>
<td>Other theories of etiology</td>
<td>21</td>
</tr>
<tr>
<td>Loss of pulmonary elasticity</td>
<td>22</td>
</tr>
<tr>
<td>Spirometric Diagnosis</td>
<td>28</td>
</tr>
<tr>
<td><strong>SECTION II</strong></td>
<td></td>
</tr>
<tr>
<td>BASIS OF PRESENT INVESTIGATION</td>
<td>34</td>
</tr>
<tr>
<td>Clinical Material</td>
<td>34</td>
</tr>
<tr>
<td>Methods Applied</td>
<td>35</td>
</tr>
<tr>
<td><strong>SECTION III</strong></td>
<td></td>
</tr>
<tr>
<td>TECHNICAL DETAILS</td>
<td>37</td>
</tr>
<tr>
<td>Spirometry</td>
<td>37</td>
</tr>
<tr>
<td>Peripheral Venous Pressure</td>
<td>38</td>
</tr>
<tr>
<td>Circulation Times</td>
<td>40</td>
</tr>
</tbody>
</table>
SECTION IV

REVIEW OF TECHNICAL PROCEDURES USED IN THIS INVESTIGATION OF CIRCULATORY DYNAMICS........... 43

Recording of Peripheral Venous Pressure ............... 43

Historical resume .................................. 43

Significance of reference level......................... 44

Consideration of variables within the control of the investigator .................. 46

Recording of Circulation Times ..................... 49

Evaluation of current methods of recording circulation times ......................... 49

Critical evaluation of circulation time as an index of the velocity of blood flow........ 56

SECTION V

RESULTS OF THIS INVESTIGATION ............... 82

Controls ............................................... 82

Emphysema ........................................... 82

Comparison of Results in Emphysema and in Controls... 84

Emphysema with Congestive Heart Failure.............. 85

Comparison of Results in the Three Groups .......... 89

Comparison of Results in Heart Failure of Emphysema with Corresponding Records in Rheumatic Heart Failure .......................... 90

SECTION VI

DISCUSSION .............................. 93

SUMMARY ........................................... 143

ACKNOWLEDGMENTS .............................. 148

BIBLIOGRAPHY ............................... 149
<table>
<thead>
<tr>
<th>TABLE</th>
<th>LIST OF TABLES</th>
<th>OPPOSITE PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Range of Reported Normal Brachial Venous Pressure</td>
<td>44</td>
</tr>
<tr>
<td>II</td>
<td>Estimated Normal Range of Human Adult Circulation Times by Representative Modern Methods</td>
<td>55</td>
</tr>
<tr>
<td>III</td>
<td>Duplicate Records at Brief Intervals of Thiamine (Arm to Tongue) Circulation Time in &quot;50 Normal Subjects&quot;, (After Swenson (1946))</td>
<td>74</td>
</tr>
<tr>
<td>IV</td>
<td>Reported Distribution of Macasol Circulation Times (Modified from Meneely and Segaloff (1947))</td>
<td>77</td>
</tr>
<tr>
<td>V</td>
<td>Reported Normal Range of Circulation Times in Children</td>
<td>80</td>
</tr>
<tr>
<td>VI</td>
<td>Frequency Distribution of Circulation Times and Brachial Venous Pressure in 50 Controls</td>
<td>82</td>
</tr>
<tr>
<td>VII</td>
<td>Circulation Times and Brachial Venous Pressure in Uncomplicated Emphysema</td>
<td>83</td>
</tr>
<tr>
<td>VIII</td>
<td>Difference Between Corresponding Means in Emphysema and Controls</td>
<td>84</td>
</tr>
<tr>
<td>IX</td>
<td>Circulation Times and Brachial Venous Pressure in Emphysema with Congestive Heart Failure</td>
<td>85</td>
</tr>
<tr>
<td>X</td>
<td>Difference Between Corresponding Means in: (a) Controls and Emphysema with Congestive Heart Failure. (b) Uncomplicated Emphysema and Emphysema with Congestive Heart Failure</td>
<td>89</td>
</tr>
<tr>
<td>XI</td>
<td>Re-Assessment of Significance of Difference Between Mean Lung to Tongue Times in the 3 Groups after Omission of the 3 Outlying Observations in Histogram (Fig: 4)</td>
<td>90</td>
</tr>
<tr>
<td>XII</td>
<td>Segmental Circulation Times and Brachial Venous Pressure in Rheumatic Heart Failure</td>
<td>91</td>
</tr>
<tr>
<td>XIII</td>
<td>Difference Between Corresponding Means in Emphysema Heart Failure and in Rheumatic Heart Failure</td>
<td>92</td>
</tr>
<tr>
<td>FIGURE</td>
<td>DESCRIPTION</td>
<td>OPPOSITE PAGE</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
<td>---------------</td>
</tr>
<tr>
<td>1</td>
<td>Spirometric Recordings in Health and in Emphysema</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>Spirometric Pattern of Emphysema</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>Spirometric Recording in Emphysema Heart Failure</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>Spirometric Recording after Recovery from Heart Failure of Emphysema</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>Frequency Diagram of Lung to Tongue Time in Controls, Uncomplicated Emphysema and Emphysema Heart Failure</td>
<td>90</td>
</tr>
</tbody>
</table>
INTRODUCTION

The lungs are the organs of ventilation and respiration; the heart applies the motive force of the circulation. Together the heart and lungs, under physiological conditions, serve basically to ensure an optimum gaseous exchange between the external environment and the circulating blood. Oxygen transfer, an integral part of this exchange, indispensibly subserves most biological functions and is, of all requirements, most urgently necessary for the continuance of life. Quantitative variation in gaseous exchange and hence in the work demanded of the organs responsible is determined, under the same conditions, by the metabolic level of the organism as a whole. The heart and lungs therefore, though anatomically distinct as other organs are, physiologically are a unity as other organs in combination are not. The efficient sustained performance of both is necessary if the respiratory requirements of the individual under all possible circumstances are to be met with the greatest economy. Then haemo-respiratory exchange is quantitatively adjustable to the prevailing level of metabolic activity by a changing volume of ventilation and a changing velocity of circulating blood.

It is a biological truism that a sublethal defect of a part evokes an adaptive effort at compensation in another part - the part best calculated to serve that end. It is reasonable therefore that
structural disease of the heart should firstly be compensated functionally by modification of effort in that chamber of the heart that can with greatest mechanical efficiency serve that purpose - so long as it is not prevented from doing so by the same disease or by reason of some other handicap; and secondly, if necessary, that it should be compensated by appropriate change in the work of the lungs. That both occur has long been an accepted fact. The greater work of the left ventricle in the presence of aortic stenosis and the hyperventilation that sometimes accompanies congestive heart failure are respective examples. It is also accepted that pulmonary disease is followed by a compensatory effort in the part of the lung or lungs not so diseased. It is equally reasonable that should the response of the lungs in these circumstances be inadequate, or to lessen their burden even if it were potentially adequate, the heart would adapt itself compensatorily in the appropriate way. Yet the heart is not usually accorded this function.

It will be argued that vesicular emphysema, a progressive disease involving both lungs in their entirety and therefore not allowing of compensation by the lungs themselves, a disease which is harmful to the individual by reason of its interference with gaseous exchange, is so compensated by the heart; that the recognized structural changes in, and
ultimate failure of, the heart in the emphysematous patient are explicable on the basis of such compensation. This possibility was tentatively suggested by Blumgart and Weiss (1927) on the strength of their pioneer observations on circulation time when they used radium C, injected intravenously, as an index of blood velocity.

The initial compensatory response of any organ is in the nature of more work (or less, if need be, but the latter will not be considered here), that is a purely functional adaptation. Should the need persist anatomical adaptation designed to maintain or to facilitate the greater effort ensues. It will be shown that co-existing with emphysema at a relatively early stage is a rapid pulmonary circulation rate, implying a more forceful ejection by the right ventricle; at a later stage the same ventricle is demonstrably hypertrophied. It is suggested that both these phenomena are compensatory in origin and that the enlargement of the right heart is not, as has been immemorially stated, determined by the greater work required to overcome the increased resistance in the pulmonary circulation, irrespective of whether such increased resistance exists or not. In other words, the right heart hypertrophies not because it must do so in order to perform its own work, but in order to preserve optimum respiration at the most economical level of energy expenditure.
Dyspnoea on effort and cyanosis are common to emphysema and congestive heart failure. The triple symptomatology of effort dyspnoea, cyanosis and peripheral oedema is characteristic of congestive heart failure. It is usually stated that in the presence of emphysema enlargement of the liver from venous engorgement or the appearance of oedema establishes a diagnosis of right heart failure (Parkinson and Hoyle, 1937; Durant, 1946). Emphysema moreover has been described as the commonest cause of cor pulmonale (Scott and Garvin, 1941; Spain and Handler, 1946; Durant, 1946).

Enlargement of the liver is ordinarily presumed from descent of its lower border. In the emphysematous patient downward displacement of this organ is a natural sequel to the changed pressure within the chest and in these circumstances it is usually impossible to determine whether it is engorged or not. It will be shown also that with emphysema as with congestive heart failure peripheral venous pressure is raised and, further, that emphysema alone can cause oedema. The differential diagnosis of advanced emphysema from congestive heart failure therefore is one of considerable difficulty. It is doubtful if in the light of current knowledge it is always possible.

From a consideration of circulation times and venous pressures an attempt will be made to establish
diagnostic criteria by which emphysema can be differentiated from the heart failure that it may give rise to and this, in turn, from heart failure occurring as an incidental but serious complication of the original disease. Rational treatment necessitates this detailed differential diagnosis.
There can be few diseases of which so much has been written as of emphysema, still fewer whose literature is characterised by so much repetition of ancient beliefs and so little regard for established truth.

Nomenclature

The word "emphysema" is of Greek origin and strictly means distension with air. It can readily be imagined that so meaningful a word would be eagerly sought after by early recorders of morbid symptoms that had little in common but mere swelling. It was so and the resulting confusion still exists. The qualifying epithets that are now triumphantly listed in every text-book of medicine are more numerous than the diseases to which they apply. Failure to standardise the nomenclature of the various types of emphysema has prevented the common understanding of any, and especially of the emphysema that matters most and forms the subject of this thesis. This disease is comprehensively referred to in this country as *generalised hypertropic vesicular emphysema* (although the adjective "hypertropic" were better omitted). The modern American equivalent is
obstructive emphysema (Kountz and Alexander, 1929; Courmand, Richards and Darling, 1939; Darley and Kauvar, 1946). It is the form of the disease commonly implied when the word "emphysema" is used without qualification and it will be so in this text. It was described as "large-lunged" emphysema by Jenner (1857) and frequently is so still. This description is picturesque but inaccurate in so far as the volume of the emphysematous lungs is not increased (Christie, 1944).

Historical Review

Evolution of modern concept of emphysema.
Laennec (1819, 1826) is universally credited with the recognition of pulmonary emphysema and he himself anticipated posterity in this respect by referring to the disease as one previously unknown ("une maladie jusqu'ici inconnue"). It was not uncharacteristic of Laennec that he chose to ignore or even to disparage much in previous or contemporary literature. To him is due the credit for establishing the diagnosis of emphysema in the living by unifying its morbid anatomy and symptomatology, but the disease certainly was not unknown before his time.

In Greek writings the word "emphysema" is used freely in the sense of intestinal flatulence and abdominal distension. It was introduced into English literature to describe tissue swelling in the
neighbourhood of surface wounds (Lovell, 1661). Lovell, apparently referring uncritically to all manner of such swelling and, no doubt, including gas gangrene, considered the cause to be entrance of air from the atmosphere by way of the wound. The word did not preserve this exclusive meaning however and it came to be used by English writers to connote the presence of air in any tissue until Watson (1764), although using it in the same sense, referred to the "truly emphysematous" lungs discovered post mortem in a patient who had had asthma for a long time. By this he implied that air had transgressed its natural confines in the lungs and escaped into the interstitial tissues. Thereafter it came to realised that the presence of air in the subcutaneous tissues was more commonly due to rupture of some part of the respiratory tract than to air entry from the atmosphere through an external wound. Many cases of subcutaneous emphysema caused in this way and diagnosed clinically were reported as a complication of prolonged labour or as a sequel to violent bouts of coughing (Louis, 1768; Simmons, 1784; Smith, 1790; Bromfield, 1790; Blagden, 1792; Halliday, 1807; Balfour, 1811; Breschet, 1815; Ireland, 1820). It was the accessible emphysema that dominated the attention of these observers and they were surprisingly
uninterested in the lungs considering that in the circumstances they regarded these organs as ruptured and leaking air. In general this concept of emphysema remained in vogue until well into the nineteenth century. Thus Townsend (1833), epitomising popular (but outmoded) knowledge of the disease, classified emphysema as:

(1) **Traumatic emphysema**, "produced by the introduction of atmospheric air into the cellular tissues, through a solution of its continuity, ..........(a) succeeding to any wound of the integuments which allows the external air to get into the subjacent cellular tissue; but (b) in a great majority of cases arising from the introduction of air into the common cellular tissue through a communication formed more or less directly with the organs of respiration"

(2) **Idiopathic or spontaneous emphysema**, caused "by the development of gas within the cells of the part"

Apart from the more common types of wound communicating with the respiratory tract and producing subcutaneous emphysema it is recorded by Rullier (1833) that the prisoners in the Bicêtre in Paris, when
they wished to change the privations of the goal for the greater comfort of the prison hospital, were in the habit of producing an alarming swelling of their face and neck by puncturing the inside of the cheek with a pin and blowing air through it. (In the course of the recent war I came across a distressing incidence of the same disease among soldiers of an alien race whose enthusiasm for the allied cause was less inspired than one would have wished). Much of what was described as idiopathic emphysema is now recognizable as having been caused by unsuspected injury to the respiratory tract as, for example, in forcible reduction of a dislocated humerus (Townsend, 1833), or by injury to the alimentary tract and abdominal parietes (von Haller, 1755; Chabert, Flandrin, and Huzard, 1806); and undoubtedly both "idiopathic" emphysema and that following external wounds did, at times, include infection with gas-forming organisms (Hunter, 1762; Huxham, 1767; Baillie, 1793).

It remained to Laennec (1826) to differentiate the pulmonary emphysemas and to apply the term vesicular emphysema (of which he recognized generalised and localised forms) in the sense in which it is used (correctly) today. What he wisely called "atrophy of the lungs" and recognised as a phenomenon of old age was subsequently confounded with the name "senile emphysema". This phrase has in turn acquired
another meaning (Freund, 1906; Loeschke, 1911; Tendeloo, 1925; Kountz and Alexander, 1932, 1934; Darley and Kauvar, 1946) and will again be referred to presently. Laennec's "hypertrophy of the lungs" later became "compensatory emphysema". He appreciated the existence of mediastinal emphysema and its potential spread to the subcutaneous tissues.

Certainly much of what had been, prior to Laennec's (1926) classification, interpreted as interstitial emphysema was in fact bullous vesicular emphysema. Laennec recognized subpleural bullae for what they were "by the circumstance that we cannot force the contained air, by pressure of the finger, to leave its place and to pass under the contiguous pleura - as would be the case if it were extravasated" (translation by Forbes, 1834). His differentiation of vesicular from interlobular emphysema was at times less astute than this. He himself actually included in his category of vesicular emphysema true extravasation of air under the pleura and regarded its occurrence as almost inevitable in the evolution of vesicular emphysema. So much so that he considered emphysema previous to this stage as "merely the exaggeration of the natural condition of the viscus,.............,yet consisting in an excessive, permanent, unnatural distension of the air cells, the air being still
contained in its proper cavities" (translation by Forbes, 1834). His definition of interlobular emphysema on the other hand was restricted to acute intra-pulmonary extravasation of air, rarely leading secondarily to the appearance of air under the pleura (the reverse sequence did not, in his experience, occur), and never following on or co-existing with vesicular emphysema. Within these limitations Laennec's (1826) description of interstitial emphysema does not significantly differ from that accorded to it today. "......... When the extravasation exists near the root of the lungs", he wrote,"it speedily extends to the mediastinum, and from there crosses to the neck and over the whole subcutaneous and intermuscular cellular substance of the body" (translation by Forbes, 1834). This and his further discussion of interstitial and mediastinal emphysema make interesting reading in view of the recent eponymous resurrection of the disease (Hamman, 1939).

Andral (1829), whose criticism of Laennec was not unprejudiced, denied the existence of pulmonary emphysema other than the interlobular variety. Laennec's vesicular emphysema he dismissed as simple hypertrophy (or, strangely enough, atrophy). The entity of vesicular emphysema was also disputed by Piedagnel (1829) but in both his and Andral's written
criticism there is in fact described the disease whose existence they were denying. Laennec's interpretation of vesicular emphysema became established and his description of the disease was in time incorporated, only too literally, in standard textbooks of medicine. It is a credit neither to the memory of Laennec nor to the enlightenment of the editors concerned that many of these books still continue to include among the outstanding facts that he established much in which he has long been shown to have been mistaken.

Pre-Laennec literature. If one gives less attention to the name (emphysema) and more to the disease the perspective differs. As long as 128 years before Laennec (1826) published his observations on emphysema Sir John Floyer (1698), in writing of the disease of horses called the "broken wind", gave a detailed account of the morbid anatomy of the lungs of a mare previously suffering from that disease. Floyer's description of these lungs is an accurate narrative of the morbid anatomy of generalised vesicular emphysema as it occurs in man, no less comprehensive than Laennec's, and one is forced to the conclusion that the broken wind of horses and emphysema of man are the same disease. This was subsequently shown to be the case (Percivall, 1823; Andral, 1829; Kountz and Alexander, 1934). Furthermore Floyer himself con-
sidered that his observations on the broken wind were equally applicable to the corresponding disease in man. "So it is in the flatulent asthma (of man)" he wrote, "the frequent nervous inflations induce at last a constant windy tumour or inflation, and it ought to be considered how far the violent coughing in lung catarrhs or the great distension of the lungs by an inflammation may strain the bladders and their muscular fibres, and thereby produce the same rupture or dilatation or herniae as happens in the broken winded. This must be observed by the help of the microscope; and if the air blown into the lobe will not be expelled thence by the natural tone or muscle of the bladders that the lobe may again subside of itself, it is certain some injury is done to the ventiducts; the bladders are either broken and admit the air into the interstices, or else they are over distended like a hernia in the peritoneum; and this will produce an inflation of the whole substance of the lungs......." This is truly remarkable reasoning for the seventeenth century. Allowing for the archaic terminology his statement of pathology does not differ much from that in text-books of today. It is well worth noting also that Floyer postulated the existence of a vesicular and an interstitial form of emphysema, yet Laennec (1826) referred pontifically to both varieties as diseases not previously described
("………et n'a été jusqu'ici exactement décrit par aucun auteur (p.289).………Je n'en connais même, aucune description exacte et faite après nature" (p. 338)). One is not even left the happy choice of assuming that Laennec was unfamiliar with the other's work for he referred cursorily to Floyer as having noticed that the lungs in a broken winded mare were "voluminous and distended with air-----but that neither he nor any previous author appears to have been acquainted with the real character of the affection=========" (Forbes, 1834). Floyer's phenomenal insight into "the real character of the affection" is exemplified by the following quotation in which he recommends artificial pneumothorax as its rational treatment: "The care of the broken wind cannot easily be projected any other way but by a paracentesis in the thorax; for if the external air be admitted it will compress the flatulent tumour------------------------------." This suggestion was either ignored or despised for more than 200 years. In 1926 Canter advocated artificial pneumothorax in the treatment of emphysema. Chrisite (1934), accepting its rationale, applied this treatment to emphysematous patients but presently desisted in view of the danger of puncturing a bulla and producing a tension pneumothorax. It is scarcely creditable to Forbes (1834), who is responsible for the English translation of Laennec, that he prefaced his reference to Floyer's suggested treatment with these words: "The following
unstable proposals for curing emphysema of the lungs seem worthy of record in this place, as a striking illustration of the absurdities into which even the most sensible practitioners could be led, before the physical researchers of the moderns had redeemed pathology from the dominion of metaphysical theory."

Other writers of the pre-Laennec period, apart from those mentioned, referred to "greatly distended" and "voluminous" lungs, recognizably emphysematous, as a post mortem finding (Bonet, 1700; Ruysch, 1721; Valsalva, 1741; Ridley, 1763; Morgagni, 1769; Herberden, 1802; Halliday, 1807; Baillie, 1807; Breschet, 1815). They were interested in the disease in so far as it caused an anatomical variation in the lungs and scarcely at all as an influence on health. When an explanation of the phenomenon was hazarded it was generally to the effect that the lungs were "over distended" by air which had escaped into the interstitial tissues, but Bailley (1807) described in detail the same three salient features of morbid anatomy in the emphysematous lungs as were subsequently emphasised by Laennec (1826), without, apparently, realising that they were all determined by the same disease.

**Histology of the emphysematous lungs.** Following Laennec's (1826) work the next significant advance in the understanding of emphysema was contributed by Rainey (1848) in observing the microscopic
anatomy of the diseased lungs. This was developed further by Rokitansky (1861) who used stained sections for the first time, and by Isaakssohn (1871) who stressed pulmonary vascular degeneration as an integral part of emphysema. The detailed histology of emphysema has been the subject of much controversy and will subsequently be referred to at length.

Pathogenesis

"It has already been shown that in the dry catarrh the smaller tubes are frequently obstructed, either by the pearly sputa or by the swelling of their inner membrane. Now, since the muscles of inspiration are numerous and powerful, while expiration, on the other hand is produced entirely by the elasticity of the parts and by the feeble contraction of the intercostal muscles, it must frequently happen that the air, which during inspiration has overcome the resistance opposed to its entrance by the humid state of the bronchial membrane and the sputa, is unable to force the same obstacles during expiration and remains therefore imprisoned in the cells, by a mechanism somewhat similar to the
valve of an air gun. The succeeding inspirations, or at least such of them as are energetic, introduces a full supply of air into the same cells, and thereby necessarily occasion their dilatation; and provided the obstruction is of some continuance, the dilated condition of the cells will be rendered permanent.-------------------------

"This (sensation conveyed to the hand when palpating the detached emphysematous lung) seems to indicate either a more difficult communication between the air contained in the air cells and that in the bronchi, or else a diminished elasticity of the air cells themselves" (Laennec, 1826; translation by Forbes, 1834).

"----------May not pulmonary emphysema be produced in the same mechanical manner in man from severe and long continued coughs? May not the temporary distension of the air cells by air or mucus give rise to their permanent dilatation? All that is necessary to ensure this result is that the elastic power naturally inherent in the air cells should be overcome and destroyed."
Respiratory obstruction. These two quotations are reasoned statements of the authors' views on the causation of emphysema. Floyer's (1698) was not substantially different from Laennec's. On the basis of mechanistic theory Laennec presumed that any condition associated with breath holding, forced breathing, or respiratory obstruction caused emphysema. All was conjecture but comprehensive enough to include much that is now established fact as well as much that is fanciful. It is significant however that the concept of expiratory obstruction as the basic cause of emphysema has been stressed from the beginning, as has the association of the disease with chronic asthma and "the dry catarrh" (Floyer, 1698; Laennec, 1826). Of "the dry catarrh" Laennec remarked that "spasmodic stricture of the bronchi is a frequent attendant" (Forbes, 1834). After this theory of obstructive causation had been re-formulated by Laennec it was vigorously assailed by Andral (1829) and Piedagnel (1829) but their criticism accords ill with their own argument for they appear largely to have misunderstood Laennec's thesis. They certainly misinterpreted it. Presently however bronchial obstruction came to be accepted as the determinant of emphysema and the view still prevails (Alexander,
Experimental emphysema. In 1865 Brown-Squard produced alveolar distension experimentally in animals by electrical stimulation of the base of the brain near the vagal nuclei. He attributed the effect to bronchospasm. Subsequently "emphysema", reputedly the same as that following asthma in man, was produced in animals by various forms of experimental respiratory obstruction (Sudsuki, 1899; Bullara, 1900; Siebeck, 1909; Harries and Chillingworth, 1924; Nissen, 1927; Loeschke, 1928; Kountz, Alexander and Dowell, 1929). In all these experiments the "emphysema" was permanent if the obstruction was continued long enough. They apparently prove the significance of respiratory obstruction in the evolution of emphysema and are eminently compatible with Laennec's theory of pathogenesis, but they also oversimplify the issue. Generalised vesicular emphysema can, and does, occur spontaneously in the absence of any demonstrable respiratory obstruction as in those acclimatised to high altitudes (Hofbauer, 1925; Campbell, 1928, 1929; Hurtado, 1932; Christie, 1944;) and, rarely, among those in an ordinary environment who have not suffered from chronic cough or asthma (Kountz et al., 1934; Christie, 1944).
Kountz and Alexander (1934) would explain these on the basis of occult bronchospasm. It is now known also, notwithstanding monotonous repetition to the contrary, that neither glass blowing nor the playing of wind instruments causes emphysema (Lomme, 1910; Becker, 1911; Tendeloo, 1925, Jagić and Spengler, 1924; Loeschke, 1928; Christie, 1944). Where respiratory obstruction does exist there are always other attendant circumstances which are not irrelevant.

Other theories of etiology. Many other theories of etiology have from time to time been advanced, usually with no more justification than is due to mere surmise. It has, for example, been said that emphysema is caused by the strain of forced inspiration (in contrast to expiration) (Gairdner, 1849), by excessive respiratory effort of a physiological kind as in strenuous employment (Durig, 1903; Hasselbach, 1908; Podkaminsky, 1929, 1930; Winglehard, 1929), by primary fixation of the thorax (Freund, 1911, 1913), spinal deformity (Loeschke, 1911), pulmonary vascular disease (Rainey, 1848; Isaakssohn, 1871; Delafie, 1885; Curschmann, 1928), imperfect nutrition of lung tissue (Villemin, 1866), infection (Minkowsky, 1912; Tomey and Grosch, 1919), and by a defect of elasticity in the lung (Andral, 1823; Eppinger, 1876; Letulle, 1928; Christie, 1934, 1944). With the exception of the last mentioned which will be presently discussed at length these
hypothetical causes are not now accorded any significant role in the genesis of generalised vesicular emphysema.

**Loss of pulmonary elasticity.** In both quotations which preface this review of pathogenesis mention is made of pulmonary elasticity. While Laennec (1826) invoked a hypothetical inelasticity of the lungs only to explain the perpetuation of alveolar distension (as emphysema) in the absence of continuing obstruction, Andral (1829) appears to have regarded pulmonary inelasticity as a necessity for the development of emphysema in all circumstances. At a later date high controversy developed over the elastic properties of the emphysematous lungs. This fruitless argument especially concerned itself with elastic tissue as anatomically demonstrable — whether in the individual with emphysema it was congenitally defective (Greenon, 1867; Bayer, 1870; Grawitz, 1892), absolutely diminished in consequence of postnatal degeneration (Füppinger, 1876; Minkowsky, 1912; Letulle, 1928), or just stretched and only apparently diminished (Klaege, 1886; Tendeloo, 1931).

It is an inescapable observation that the healthy lungs possess qualities of elasticity. (When removed from the body they are of smaller volume than they are in vivo). In the living body the healthy lungs are distended, subject to elastic stresses,
and their volume changes continuously in the act of breathing. In any instant the degree of distension is a function of the particular elastic modulus. Indirectly it has been shown many times that, within physiological limits, the elasticity of the lungs must be nearly perfect in that distension is proportional to the stress and there is no appreciable "set" (Heynsius, 1882; Liebermeister, 1907; Jaquet, 1908; Bernoulli, 1911; Romenoff, 1911; Cloetta, 1913). This conforms to the universal belief that expiration is entirely passive; the lungs return to their original volume by reason of their own elastic recoil. This ceases to be true when the lungs are diseased.

It is ancient knowledge that expansion of the lungs is dependent on a closed pleural cavity. Hippocrates (460 B.C.) records that it was common to execute criminals by inflicting an open wound of the chest and Celsus (25 B.C.) was aware of the danger of open pneumothorax. Vesalius (1543) observed that when the costal pleura was opened the lung collapsed and the heart worked at a disadvantage; eventually, if unrelieved, the heart ceased to beat. He realised that life could be saved by introducing a reed into the trachea and blowing into this rhythmically, that is by positive pressure breathing. In contrast, it
has long been noted at autopsy that emphysematous lungs do not collapse when the chest is opened as normal lungs do, and this has been associated with a diminished elasticity (Floyer, 1698; Bonet, 1700; Ruysch, 1721; Watson, 1764; Morgagni, 1769; Halliday, 1807; Baillie, 1807; Breschet, 1815; Laennec 1826; Andral, 1829).

In 1820 Carson measured the elasticity of the lungs after death by connecting a water manometer to the trachea and recording the pressure generated when the pleural cavity was opened to the atmosphere. This experiment has been repeated many times with little variation in technique on both healthy and diseased lungs (Donders, 1853; Perls, 1869; Heynsius, 1882; Romanoff, 1911; von Neergaard, 1929; Van Allen and Wu, 1932), but the results obtained are not applicable to the living lung if only because pulmonary elasticity changes considerably immediately after death (Van der Brugh, 1900; Christie and McIntosh, 1934). Quantitative estimation of the elasticity of the emphysematous lungs was fallacious for the same reason (Tendeloo, 1925; Loeschke, 1928; Thies, 1932). Rohrer (1916) claimed to derive a measurement of pulmonary elasticity in vivo from manometric recordings of intratracheal pressure during obstructed expiration. He concluded that there was a diminution of elasticity in emphysema.
The intra-pleural pressure is the tension on the surface of the lungs and on the parietal pleura, either when the lungs are in movement (dynamic pressure) or at rest (static pressure). This pressure, like the lung volume, changes continuously during the respiratory cycle except in the momentary pauses at the end of inspiration and expiration. It was for the first time recorded in the living by Aron in 1891. Normally the intra-pleural pressure is less than atmospheric pressure and usually fluctuates around a mean of -5 cm. of water (Aron, 1928; Christie and McIntosh, 1934). Presently it was discovered that in the experimentally produced emphysema of animals intra-pleural pressure was to a less extent subatmospheric than it ordinarily is (Nissen and Cokkalis, 1925; Kountz, Alexander and Dowell, 1929). The same change of pressure towards positivity was then shown to be a feature of spontaneously occurring emphysema in man where, in fact, the pressure varies little from atmospheric (Kountz, Pearson and Koenig, 1932). In 1939 Christie and McIntosh devised a means of accurately measuring pulmonary elasticity (and distensibility) by simultaneous recording of intra-pleural pressure and tidal air. Using this method they demonstrated that, under physiological conditions, (1) the degree of distension of the lungs is proportional to the change in intra-pleural pressure, that is the stress is proportional to the strain,
(2) if distension of the lungs be maintained the intra-pleural pressure remains constant, and (3) there is no "set" when the lungs are allowed to deflate. They thus proved that the elasticity of the healthy lung in vivo is perfect. Christie (1934) then demonstrated that invariably in emphysema there is almost complete loss of pulmonary elasticity and, further, that this is the case at a comparatively early stage of the disease. He showed also that the loss of elasticity could be more simply deduced from the spirometric record alone. These observations have been amply confirmed (Cournand, Richards and Darling, 1939; Paine, 1940; Christie, 1944) and it is probably true to say that the simpler procedure is indispensable to the unequivocal diagnosis of emphysema (Christie, 1944). It is Christie's (1944) contention that loss of elasticity is the cause of emphysema.

There are now none who will not agree that the emphysematous lungs are inelastic, but there is yet disagreement over the significance of the loss of elasticity in the genesis of the disease. Although it has always been accepted that chronic bronchitis or bronchial asthma (or both) are, almost invariably, precursors of generalised vesicular emphysema it remains to establish the mechanism whereby emphysema develops from these. Of the many theories suggested
in the past two only have survived until now. To
some respiratory obstruction is still paramount in
the causation of the disease. On this basis air is
"trapped" in the air sacs because these cannot be
emptied; the alveoli therefore become over-distended
and the "stretching" of the alveolar walls in turn
leads to functional impairment of elasticity and
eventual degeneration of elastic tissue (Kountz and
Alexander, 1934; Cournand et al., 1939; Darley and
Kauvar, 1946). To others loss of elasticity is
primary in that it is the cause, not the consequence,
of alveolar distension and formation of bullae. The
loss of elasticity (which involves the visceral pleura
and the costal and vertebral cartilages as well as
the lungs) is itself caused directly by the frequently
repeated stress and strain occasioned by the coughing
of the bronchitic or the laboured breathing of the
asthmatic. In each case there is "a wave of pressure
change passing out from the bronchi to the periphery
of the lung. "--------the lung (during the act of
coughing or obstructed breathing) is compressed and
not in any sense distended" (Christie, 1944). This
concept of "compressive" injury to the lungs accords
perfectly with the mechanism of coughing in which,
when the glottis is closed, the lungs are forcibly
compressed by the action of the expiratory muscles
and the pressure of air in the alveoli may exceed
50 mm. of mercury (Kountz and Alexander, 1934;
Rasmussen and Adams, 1942). In bronchial asthma there
is a similar change of intra-alveolar pressure with each (active) expiration and, although it may occur less abruptly than in the explosive act of coughing, it occurs more frequently (v. Neergaard and Wirz, 1927; Hartwish, 1930). The effect over a long period of time is the same — the lungs lose their elasticity and that, irrespective of theory, is emphysema. The experimental production of emphysema by tracheal obstruction can be explained on the same basis (Paine, 1940).

**Spirometric Diagnosis**

Notwithstanding authoritative pronouncements by Cabot (1927) Hurtado and Boller (1933) and by Christie (1944) on the diagnosis of emphysema, standard text-books continue to equate the diagnosis with the barrel-chest phenomenon. True emphysema can exist with a chest of normal shape and size, and a barrel-shaped chest can exist in the absence of emphysema (Cabot, 1927; Davidson, 1936; Hurtado and Boller, 1933; Roelsen, 1938; Christie, 1944). Only a small proportion of emphysema discovered at antopsy has been diagnosed during life (Christie, 1944). The spinal deformity of old age and, less commonly, corresponding postural skeletal change in younger people causes a barrel-shape deformity of the thorax by increasing its antero-posterior
diameter (Kountz and Alexander, 1932, 1933, 1934; Darley and Kauvar, 1946). The lungs adapt themselves secondarily to the deformed chest (as would be the case whatever the deformity) but this does not constitute emphysema in the sense defined. It is the custom in America, however, to refer to this as senile or postural emphysema according to the age of the patient (Kountz and Alexander, 1934; Darley and Kauvar, 1946). It is what Laennec (1826) called "hypertrophy of the lungs".

Loss of pulmonary elasticity is the cardinal lesion of emphysema (Christie, 1944). The absence of elastic recoil in the emphysematous lungs can be demonstrated in the spirometric pattern of the breathing (Christie, 1934, 1944). If the emphysematous patient inspires deeply the succeeding expiration does not return to the previous respiratory level as it does in the normal individual. A new and higher level is established or, more characteristically, successive expirations are recorded as extending progressively lower until the original level is reached. The inelasticity of the emphysematous lungs is further reflected in the spirometric tracing by the contrast between a maximum expiration following quiet breathing and the same following a maximum inspiration. With normally elastic lungs these are more or less equal; in the emphysematous individual the former is considerably greater than the latter. It follows that
Figure 1 Overleaf
Figure 1

Spirometric recording from healthy individual (above) and emphysematous patient (below) of comparable age, height and weight. The lower record shows, in addition to the obvious reduction in vital capacity, complementary and reserve airs, (1) the step-like descent to the original expiratory level after a maximum inspiration, (2) the greater reserve air following upon quiet breathing than succeeding a forced inspiration, (3) the varying level of resting respiration.

C = complementary air; VC = vital capacity; R = reserve air.
the reserve air measured after a period of quiet breathing is greater than the reserve air following a maximum inspiration. After a maximum inspiration the reserve air may, in fact, be represented by a negative quantity. These phenomena can only be due to overstretching of lungs whose elasticity is impaired. A third feature of the spirometric record is the irregularity of the respiratory level in quiet breathing. These facts are illustrated in Figures 1 - 4 (opposite pp. 30, 35 and 87).

Cournand, Richards and Darling (1939) stress retardation and prolongation of expiration as the most constant spirometric change in emphysema. In mild cases this is seen only in deep breathing but as the disease advances it becomes evident in quiet breathing also. This is the equivalent of the prolonged expiratory murmur which is included as a sign of emphysema in every text-book of medicine and of the irregularity in the spirometric expiratory level which has been interpreted as due to expiration mediated by active muscular effort (Scott, 1920; Christie, 1934). Cournand, Richards and Darling (1939) also point out the existence of an "oxygen deficit" in advanced emphysema as indicated by the greater quantity of oxygen absorbed temporarily when the patient breathes pure oxygen instead of air.

A further characteristic of the patient with emphysema is his inability to hyperventilate. He
cannot increase pulmonary ventilation as the normal individual can on breathing carbon dioxide (Scott, 1930; Davies, Brow and Binger, 1925; Christie, 1934) or on exercising (Hurtado, Fray and McCann, 1933; Hurtado and Boller, 1937). He is unable to increase both the rate and depth of breathing simultaneously; the one varies inversely with the other (Kaltreider and McCann, 1937).

The respiratory efficiency of the emphysematous individual can be improved by parenteral injection of adrenaline (Kountz and Alexander, 1934) or aminophylline. Quantitatively and qualitatively the spirometric tracing is altered towards the pattern of normality. Cournand, Richards and Darling (1939) argue that the effect of adrenaline in augmenting expiration in the emphysematous patient conflicts with Christie's (1934) conception of loss of pulmonary elasticity as the basis of all the variations mentioned. They state that since the "retractibility" of the lungs can be restored by adrenaline (as they demonstrate) "it is probable that the loss of retractibility is due to bronchiolar obstruction (with air trapped beyond the closed bronchioli) rather than to an irreversible loss of elasticity............."

There is some evidence, which is being developed further, that spirometric changes similar, if not identical, with those described above as characteristic of emphysema may be produced by functionally
over-distended lungs in the absence of irreversible destruction of elastic tissue. (This refers, of course, to a chronic syndrome and excludes acute asthma and respiratory obstruction from obvious cause). If this is true it may explain the effect of adrenaline in restoring the expiratory efficiency of some cases, diagnosed as emphysema, to a completely normal level. Blumgart and Weiss (1927) consciously included such in their diagnosis of emphysema and remarked that "clinical emphysema is not necessarily based on morphological changes in the lungs but is often a purely functional entity".

Christie (1944) however offers a different explanation for the (similar) beneficial effects of ephedrine in relieving the dyspnoea of emphysema. It is that "the bronchioles leading to the over-distended air sacs and bullae are less capable of changes in calibre than those leading to healthier parts of the lung; bronchospasm, although not clinically manifest, would in this case increase the proportion of the inspired air deflected to these useless parts of the lung, and the relief of bronchospasm with ephedrine would improve the efficiency of ventilation and thus relieve dyspnoea". It is accepted, therefore, that the pharmacological effect of all the drugs mentioned as causing symptomatic improvement in emphysema is dilatation of bronchioles, but views differ over the distribution, the significance,
and even the existence of bronchospasm. The opinion expressed by Cournand, Richards and Darling (1939) conforms to current American statement on the genesis of obstructive (sic) emphysema (Kountz and Alexander, 1934; Darley and Kauvar, 1946). Even the relaxation of a normal degree of bronchiolar tonous however would improve the ventilation of non-emphysematous alveoli; there is no need, in explaining the undoubtedly beneficial effect of those drugs in emphysema, to postulate an abnormal degree of bronchiolar constriction.

Much that might pertinently be included in the section now ending, especially the historical review of emphysema in its relation to heart disease, is, to avoid repetition, deferred to Section VI, headed Discussion, from which it is inseparable.
BASIS OF PRESENT INVESTIGATION

This investigation arose out of a more comprehensive one designed to assess the changes in the dynamics of the pulmonary circulation produced by congestive heart failure from different causes. The emergence of features peculiar to heart failure caused by emphysema clearly made it necessary to establish corresponding standards for emphysema itself. The more limited research that ensued forms the subject of this thesis.

Clinical Material

The investigation embraces (within the limitations specified below) representative groups of (1) uncomplicated emphysema, (2) emphysema with congestive heart failure and (3) healthy adults. Those included in the third group, 50 in number, were "normal" in the sense that they had no recognizable disease; they serve as controls.

All of 52 cases of emphysema included in this series conformed to the diagnostic criteria enunciated by Christie (1934, 1944). All had "dyspnoea on exertion, of insidious onset, not due to bronchospasm or left ventricular failure"; all had had chronic bronchitis or asthma or both for a consider-
Figure 2 Overleaf
Figure 2.

Spirometric pattern of emphysema. The inelasticity of emphysematous lungs is reflected in the step-like descent to the previous respiratory level after a maximum inspiration, the smaller reserve air following maximum inspiratory disensit of the lungs and the irregularity of the respiratory level. Qualitatively this record is similar to Figure 1 but the degree of emphysema is less severe.

C = complemental air; VC = vital capacity; R = reserve air.
able period of time; and all had some of the physical signs usually attributed to emphysema. In passing, it may be mentioned that a most useful sign is paradoxical movement of the costal margin (Durant, 1946). The ultimate diagnosis in each case, however, was based on the spirometric pattern of breathing (pp. 28 - 29 and Figs. 1 - 4). By the same standards emphysema was excluded in the controls.

A fourth group of 40 patients with rheumatic heart failure, who were investigated at the same time, will be referred to briefly by way of comparison.

Methods Applied

Peripheral venous pressure, arm to tongue, arm to lung and, by deduction, lung to tongue circulation times were measured in each case. Apart from clinical examination almost all patients, as distinct from controls, were examined radiologically and electrocardiographically, but this was done in the course of a clinical routine and not designed as part of a specific investigation. In some of the controls and patients of both groups venous pressure was recorded during the Valsalva experiment. Vital capacity, complemental air and reserve air were estimated in all groups. These measurements were
made on a recording spirometer by means of which also quiet breathing was registered graphically. Static intra-pleural pressures were recorded in a large proportion of patients in groups 2 and 3. The recordings of pleural pressure and of the subdivisions of lung volume will not be given in detail for they differ in no way from what is already well established (Christie, 1934, 1944). The constant variation in pleural pressure that is inseparable from emphysema has been discussed in detail (pp. 25-26). It has been amply confirmed in the course of this investigation.
SECTION III

TECHNICAL DETAILS

Spirometry

The respiratory pattern of each patient (including vital capacity, reserve air, and complemental air) was registered graphically with a McKendrick recording spirometer as ordinarily used in the determination of basal metabolic rate. The spirometer was charged with oxygen. By careful adjustment of the mouth piece and occlusion of the nose with a suitable clip exclusive spirometric breathing was ensured. The recording was always done during the same two-hour period of day (between 10 a.m. and noon), never less than two hours after a meal. The patient, previously attuned to the apparatus and, so far as possible, relaxed physically and mentally, was in bed, supported in the position of 45 degrees recumbency with the lower limbs extended. This position was chosen as being least trying to the whole range of patients subjected to it. (The same was used for all other investigations to be mentioned.) The constancy of circumstances has its relevance in the known variation of lung volume and its subdivisions with posture (Panum, 1868; Bohr, 1907; Hasselbach, 1908; Christie and Beams, 1922; Rabinowitch, 1923; Meakins and Davies, 1925; Wilson, 1927; Livingston, 1928; Meakins and Christie, 1929; Christie, 1934; Hurtado and
Boller, 1933; Christie and McIntosh, 1934; Kaltreider and McCann, 1937), with fatigue (Peabody and Sturgis, 1921), excitement, some forms of external stimuli (Bittorf and Forschbach, 1910; Christie, 1932) and, naturally, with exercise (Kaltreider and McCann, 1937). The respiratory level is also modifiable by the degree of respiratory resistance (Bittorf and Forschbach, 1910; Bass, 1925; Thiel, 1929), but the small resistance implied in breathing through a spirometer or in changing from nose to mouth breathing is not in this respect significant (Greene, 1933). In fact the resistance in the spirometric circuit never exceeds 0.5 cm. of water (Christie, 1934).

**Peripheral Venous Pressure**

In the present instant venous pressure was recorded directly (Hales, 1733; Moritz and von Tabora, 1910) as follows: The positioning of the patient was as described for spirometry, that is with the trunk supported at 45 degrees and the lower limbs extended. Physical relaxation and peace of mind were aimed at as before. The arm and shoulder were bared, abducted to 45 degrees, and supported so that the site of vein puncture in the antecubital space was in the same horizontal plane as the sternal angle. (An antecubital vein was used in all but a single instant which will be mentioned). This plane was defined by using
a rigid 1-metre rule carrying a spirit level.

A 20.cc. two-way Record syringe fitted with a 20-gauge needle was partly charged with 3.8 per cent sodium citrate solution and the vein punctured. A graduated glass manometer of 2mm. bore was then attached by rubber tubing, 20 cm. long and of 3mm. bore, to the lateral limb of the syringe. By manipulating the tap the syringe and its contents could then be placed in continuity with the needle in the vein or with the manometer; or the manometer could be exclusively connected to the needle. A small quantity of citrate solution was injected from time to time into vein and manometer to prevent clotting. In the recording of venous pressure zero level of the manometer, the site of puncture and the sternal angle were in the same horizontal plane. A tourniquet was used and the needle was always inserted in the direction of blood flow. As with the spir- ometric recordings all the observations were made at the same period of day, i.e. between 10 a.m. and 12 noon, but at a time sufficiently remote from the patient's hazard with the spirometer to prevent any interference from that experience. After the vein had been punctured not less than 15 minutes were allowed to pass before the basic venous pressure was registered. When the venous pressure at rest was established the abdomen (or liver, it matters not
which) was compressed with the palm of the hand and any change in antecubital venous pressure noted (Winsor and Burch, 1946).

**Circulation Times**

The arm to tongue time was measured with decholin (which is a 20 per cent solution of sodium desoxycholate), originally used for this purpose by Winternitz, Deutsch and Brull (1931). Their use of the drug for recording circulation time was a natural sequel to the work of Neubauer (1923) who, in his search for choleretics, discovered that this bile salt could be injected intravenously in the concentration mentioned without any harmful effect, and that its intravenous injection was promptly followed by the appreciation of its characteristic bitter taste in the individual injected.

The arm to lung time was estimated by the method of Hitzig (1934).

When the venous pressure recording was completed the 2-way syringe was detached from the needle and replaced by a 5cc syringe containing that quantity of decholin. The patient remained in the same position as before. The nature of the test, what to expect and what was expected of him were explained to the patient in detail. It is considered
that this is one of the fundamental requirements of the test and demands much patience of the investigator. The injection was made as rapidly as possible and a stop watch set going when 2.5 cc. or half the injection had left the syringe. The watch was stopped when the patient indicated that he recognised the bitter taste of decholin. This ended, the syringe was again detached and replaced by another containing 0.4 cc. ether and 0.4 cc saline. Previously the patient had been familiarised with the smell of ether and again the details of the co-operation required of him were explained. As before, the stop watch was set going when half the injection had been given and stopped at the moment when the odour of ether was appreciated by the patient or the observer, whichever occurred first. Almost invariably the patient's reaction preceded the observer's.

The lung to tongue time is calculated as the difference between the arm to tongue and arm to lung times.

In every individual included in the present investigation the first recording of both decholin and ether times was discarded, irrespective of what was thought of its accuracy, and a second made 24 hours later.

The choice of mid-injection as zero of the time measurement is entirely arbitrary. Possibly it is
less open to criticism than estimating the time from
the beginning of the injection (Blumgart and Weiss,
1927, 1928; Tarr et al., 1933; Fishberg, Hitzig and
King, 1933) or the end (Winternitz et al., 1931;
Nylin and Malmstrom 1942; Gernandt and Nylin, 1946).
This will again be referred to below.

Each patient was investigated as indicated on
one or more occasions during a single period in which
he or she was under hospital care. The group of
emphysema is represented by 50 observations in each
test category, that of emphysema heart failure by 27,
and the control group by 50. The age and sex dis-
tribution in each group, as will be shown, is suffic-
iently similar to preclude significant variation in
circulation time (Blumgart, 1931; Tarr et al., 1933)
or venous pressure (Winsor et al., 1946; Wiggers,
1947) on this account alone.

Many patients now included/known of old and had
previously been investigated in the same way, but
observations made outside the period of planned in-
vestigation are excluded from the statistical analysis.

Previous observations however will occasionally be
referred to in the text in so far as that may be
strictly relevant to the argument that is being
developed.
REVIEW OF TECHNICAL PROCEDURES USED IN THIS INVESTIGATION OF CIRCULATORY DYNAMICS

Recording of Peripheral Venous Pressure

Historical resume. The direct method of recording venous pressure was used for the first time, so far as is known, by Hales (1733). He cannulated the left jugular vein of a mare which was lying on its right side and measured the distance to which the blood rose in a vertical glass tube. The same method was applied to man by Moritz and von Tabora (1910). They inserted a needle connected to a saline-filled manometer into a median basilic vein and allowed the saline to flow into the vein until a constant level was registered on the manometer. Taking zero reference level as a horizontal plane 5 centimetres dorsal to the fourth costo-sternal junction with the patient in the supine position, the vertical height of the residual column of saline in the manometer above this level represented the venous pressure. It is relevant to mention in passing that the indirect method of recording venous pressure in man had been in use for a considerable time previously (von Basch, 1904; Frey, 1902; von Recklinghausen, 1906; Sewall, 1906; Hooker and Fyster, 1908). By this method venous pressure was taken as the equivalent of the pressure
<table>
<thead>
<tr>
<th>Method</th>
<th>Reference Level</th>
<th>Position of Patient</th>
<th>Brachial Venous Pressure: Range in mm. saline, water or blood</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct 5 cm. below front of sternum at level of 4th. costal cartilage</td>
<td>Supine</td>
<td>10 - 90</td>
<td>Saline</td>
<td>Morris and von Tabora (1916)</td>
</tr>
<tr>
<td>Direct 4th. costo- sternum junction</td>
<td>Supine</td>
<td>Mean 77</td>
<td>Blood</td>
<td>Berger (1927)</td>
</tr>
<tr>
<td>Indirect 4 - 5 cm. below right auricle</td>
<td>?</td>
<td>50 - 90</td>
<td>Blood</td>
<td>Burst and Brand (1907)</td>
</tr>
<tr>
<td>Direct Lower border of Manubrium sterni</td>
<td>Body horizontal, vertical or intermediate position</td>
<td>Approximately atmospheric pressure, usually just below</td>
<td>Lewis (1920)</td>
<td></td>
</tr>
<tr>
<td>Indirect Sterno-clavicular joint.</td>
<td>Sitting</td>
<td>20 - 120</td>
<td>Water</td>
<td>von Recklinghausen (1906)</td>
</tr>
<tr>
<td>Indirect Midway between bifurcation and back</td>
<td>Supine</td>
<td>20 - 120</td>
<td>Water</td>
<td>von Recklinghausen (1906)</td>
</tr>
<tr>
<td>Indirect Midway between tip of sternum and back</td>
<td>Sitting</td>
<td>20 - 160</td>
<td></td>
<td>Hooker (1912)</td>
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<tr>
<td>Indirect Midway between costal angle and back</td>
<td>Supine</td>
<td>50 - 160</td>
<td>Mean 180</td>
<td>Clark (1918)</td>
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<tr>
<td>Indirect 'Level of right auricle'</td>
<td>Sitting</td>
<td>90 - 120</td>
<td>Blood</td>
<td>Frey (1908)</td>
</tr>
<tr>
<td>Indirect 'Level of heart'</td>
<td>Sitting</td>
<td>40 - 90</td>
<td></td>
<td>Seward (1906)</td>
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<tr>
<td>Direct Anterior axillary line</td>
<td>Supine</td>
<td>50 - 75</td>
<td>Saline</td>
<td>Harris (1928)</td>
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<tr>
<td>Direct Junction of anterior and middle thirds of thoracic diameter</td>
<td>Supine</td>
<td>45 - 130</td>
<td>Saline</td>
<td>Grifith, Chamberlain and Ritchie (1926)</td>
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<tr>
<td>Direct 2.5 inches posterior to angle of Louis</td>
<td>Supine</td>
<td>40 - 160</td>
<td>Water</td>
<td>Young (1928)</td>
</tr>
<tr>
<td>Direct 8 cm. below sternum (unqualified)</td>
<td>Supine</td>
<td>100 - 140</td>
<td>Blood</td>
<td>Taylor, Thomas and Schiefer (1920)</td>
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<td>Direct Mid-axillary line</td>
<td>Supine</td>
<td>40 - 100</td>
<td>Blood</td>
<td>Gibson and Evans (1927)</td>
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<td>Position</td>
<td>Measurement</td>
<td>Description</td>
<td>Reference</td>
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<td>Direct, supine</td>
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<td>50 - 90, blood</td>
<td>Direct, supine</td>
<td>Hurst and Brand (1927)</td>
<td></td>
</tr>
<tr>
<td>2.5 inches posterior to angle of Louis</td>
<td>60 - 120, saline</td>
<td>Direct, supine</td>
<td>Griffith, Chamberlain and Kendrick (1924)</td>
<td></td>
</tr>
<tr>
<td>8 cm. below sternum (unqualified)</td>
<td>100 - 140, blood</td>
<td>Direct, supine</td>
<td>Young (1928)</td>
<td></td>
</tr>
<tr>
<td>Mid-axillary line</td>
<td>40 - 100, blood</td>
<td>Direct, supine</td>
<td>Taylor, Thomas and Schleseter (1923)</td>
<td></td>
</tr>
<tr>
<td>4th intercostal space at sternal margin</td>
<td>50 - 140, water</td>
<td>Direct, supine</td>
<td>Winsor and Burch (1945, 1946)</td>
<td></td>
</tr>
<tr>
<td>100 mm. anterior to skin of back</td>
<td>50 - 150, water</td>
<td>Direct, supine</td>
<td>Lyons, Kennedy and Burwell (1928)</td>
<td></td>
</tr>
</tbody>
</table>
required to collapse a superficial vein or just to prevent filling of a vein that had previously been emptied. A reference level was necessary as with the other.

**Significance of reference level.** It is unfortunate that the value of recorded estimates of venous pressure is vitiated by reason of their being made under conditions that are not comparable. Apart from variation in technique, investigators have been in the habit of choosing their own standard of reference or zero level. At least eighteen different zero levels have been used in the determination of peripheral venous pressure (Table 1). Some writers have described their point of reference vaguely as "heart level" or "level of right auricle" and others have omitted to mention any level at all. The result is that the figure expressing venous pressure, even under stated conditions, does not convey a meaning which is intelligible in the sense that the corresponding figure for arterial systolic or diastolic pressure is.

The necessity of establishing an accurate reference level is the necessity of correcting for hydrostatic effect. The wide scatter over the chest wall of the many levels that have been used represents a vain attempt to define a surface projection of the computed zero level within the circulation. Assuming that the latter were known and invariable it is
doubtful if, short of strict individual localisation by X-ray screening, any definable surface equivalent would apply with any accuracy to a significant proportion of mankind. But it is not known and the probability is that it is not determined by anatomical considerations alone (Clark, Hooker and Weed, 1934).

It was for long believed that the junction of the superior vena cava and right auricle represented a true zero reference level but recently Courmand (Wiggers, 1947) has suggested that the apex of the right ventricle is, dynamically, more likely to do so.

Winsor and Burch (1945) introduced the phlebostatic level which is a horizontal plane through the axis of intersection of a frontal plane passing midway between the base of the xiphisternum and the dorsum of the chest and a cross-sectional plane passing through the fourth intercostal space close to the sternum. They state that the use of the phlebostatic level as zero reference provides measurements of venous pressure in normal subjects which are comparable in the recumbent and sitting positions.

It is highly desirable that the correct zero level should be established but in the meantime almost any reasonable level, so long as it is constantly applied to a standard posture, will allow of comparable recordings even if the pressure as recorded is not dynamically accurate. This latter qualification must
be accepted or the measurement of peripheral venous pressure abandoned until such time in the future as an unassailable technique has been evolved. Moritz and von Tabora (1910), in the first direct measurement of venous pressure in man, based their manometric zero on the right auricle which they equated with a surface level 5 cm. dorsal to the fourth costosternal junction in the recumbent position of the patient. Lewis (1930) chose the sternal angle and, irrespective of the interpretation of circulatory dynamics underlying his choice, it is as suitable for the recording of peripheral venous pressure as any introduced afterwards, and it is more simple to apply than any yet described.

Consideration of variables within the control of the investigator. In the present investigation a 20-gauge needle was used throughout although, as pointed out by Lyons, Kennedy and Burwell (1938) with some reservation and by Winsor and Burch (1946) with none, the size of the needle does not affect the recorded venous pressure. The capillarity of manometer and rubber tubing, the same on all occasions, was not taken into consideration in registering the figure for venous pressure. The reason will be apparent below.

That the needle remains in the vein and that there is no obstruction between it and the manometer
can be assumed from the small rise and fall of pressure respectively during expiration and inspiration and (more reliably) from the variation with change in position of the limb. When the arm is depressed the venous pressure rises, when the arm is elevated it falls, the change being equivalent to the hydrostatic effect (Doupe, Krynauw, and Snodgrass, 1938).

The degree of abduction of the arm directly modifies brachial venous pressure. Brandt and Katz (1931) pointed out that abduction of the arm alters the anatomical relationship of the clavicle to the first rib and subclavian vein. Holbrook (1938) showed that abduction to 90 degrees or more produced abnormally high figures for venous pressure recorded from an antecubital vein. Lyons, Kennedy and Burwell (1938) found that "in a fair majority of cases" brachial venous pressure varied with the degree of abduction at the shoulder, and concluded that the lowest readings were obtained with 45 degrees abduction. The concept of costo-clavicular compression of the neuro-vascular bundle was elaborated by Walshe, Jackson and Wyburn-Mason (1944) in the interpretation of pressure effects produced at the upper thoracic outlet. More recently however Telford and Mottershead (1947) convincingly demonstrated that in no circumstances does the clavicle approach the first rib during movement at the shoulder but that, among other
effects, the subclavian vein is compressed against the first rib by the tendon of the subclavius muscle when the shoulder is abducted or retracted.

According to Winsor and Burch (1946) venous pressure varies throughout the day and is higher in the morning than in the evening; the pressure is greatest immediately after insertion of the needle and settles down to a constant level within a period of four minutes, is higher in males than in females, and is higher when the needle is inserted against the blood stream than with it. Of these variations the most important is the temporary increase of pressure immediately after vein puncture, and it cannot be accepted that the pressure always falls to its basic level within four minutes. In the present series a period not less than fifteen minutes was allowed to elapse before the final reading was taken. Lyons, Kennedy and Burwell (1938) suggest that the size of the needle influences the time required before a constant level is reached. Wiggers (1947) comments that the sex and diurnal variations are probably fortuitous.

Abdominal compression in the normal subject causes a slight fall in antecubital venous pressure or no significant change (Winsor and Burch, 1946), whereas in the presence of right ventricular failure a considerable increase in pressure occurs. Moreover, such increase may occur and connote congestive failure at a time when venous pressure as ordinarily estimated
is within normal limits. Winsor and Burch (1946) have observed that in the sitting position antecubital venous pressure is precisely the same irrespective of whether the trunk is supported or not, and whether the legs are extended or flexed; and that muscle tension in the legs, though increasing the pressure in the great saphenous vein at the ankle, does not alter the pressure in the antecubital vein.

**Circulation Times**

Evolution of current methods of recording circulation times. "The circuit of blood", wrote Harvey in 1628, "is accomplished now more rapidly, now more slowly according to the temperament, age, etc. of the individual, to external and internal circumstance, to naturals and non-naturals, sleep, rest, food, exercise, affections of the mind and the like." Notwithstanding his appreciation of the varying velocity of blood flow Harvey made no attempt to measure it.

Hales (1733), from his measurements of the capacity of the left ventricle, the diameter of the aorta and the heart rate, calculated the velocity of blood flow in the aorta of the horse. Directly, by microscopic observation, he measured the velocity in the pulmonary capillaries of the dog.
In 1827 Hering devised a technique of measuring blood velocity by introducing a recognisable foreign substance into the blood stream and noting the time required for this to travel from one point of the vascular system to another. Although his observations were limited to the experimental animal his method provides the prototype of all modern techniques of estimating circulation time in man. He injected a solution of potassium ferrocyanide into a vein in the horse and determined the time of arrival of the drug at the distal point by bleeding the animal at that point and applying the Prussian blue reaction to successive samples of blood. He estimated in this way that the time required for the injected substance to pass from one jugular vein to the other was 26.2 seconds. Vierordt (1958) attempted to improve on Hering's (1827) method by using an elaborate piece of mechanism calculated to increase the accuracy of recording the end point. This consisted of a number of small sampling cups attached to the edge of a disc which revolved at a known uniform speed. It was so designed that when suitably positioned successive cups received an adequate sample of blood leaving the cut vessel at intervals of one second. The presence of potassium ferrocyanide was detected as before. Vierordt by this means studied the velocity of blood flow in a greater variety of animals than did Hering but accuracy was lacking to both. From his observations on animals of different sizes and under varying
conditions Hering computed that the circulation time in man from one external jugular vein to the other was 23.1 seconds at a heart rate of 72 per minute.

In 1850 Volkman designed a cumbersome apparatus for recording blood velocity directly. A pendulum-like instrument was placed in the lumen of a blood vessel and the velocity of blood flow at that point was calculated from the movement imparted to the pendulum. For obvious mechanical reasons, especially the inertia of the instrument, the method was unsound and the results erroneous.

In 1893 Stewart used hypertonic saline solution for estimating circulation times in animals. The saline was injected into a vein and its arrival in a chosen distal vessel was recognised by a change in the electrical conductivity of the blood in that vessel which was placed between two non-polarizable electrodes. Stewart (1912) also used injections of methylene blue for the same purpose, observing by transillumination the time at which the dye appeared in the common carotid artery.

In 1912 Bernstein attempted to measure the velocity of blood flow in man by getting the subject to breathe a mixture of air and 5-7 per cent carbon dioxide, noting the time laping before the depth of respiration became increased. He considered that
this interval represented the circulation time from the pulmonary capillaries to the respiratory centre in the medulla. Apart from other sources of error the method was impracticable in patients with emphysema. The next advance was when Koch in 1922 reported on his measurements of the circulation time in man by dye injection as had previously been done on animals. His method was to inject 1.0 cc. of a 1.6 per cent solution of fluorescin into an antecubital vein and take samples of blood at intervals of 5 seconds from the corresponding vein in the other arm until fluorescin was recognizable in the blood withdrawn. The potential error was considerable. Subsequently congo red was used instead of fluorescin by Klein and Heineman (1929). This dye had no particular advantage over the other.

Meldoesi (1925) and later Koch (1928) modified Stewart's (1893) method involving the injection of hypertonic saline and applied it to man. In each case the time of arrival of the salt solution in the corresponding contralateral vein was detected by means of a galvanometer connected to an electrode which had been inserted through the skin and brought into contact with the vessel.

The numerous modern methods of measuring circulation time as a practicable clinical test have evolved from the stimulus provided by Blumgart, Yens and
Weiss in 1927 (Blumgart and Yens, 1927; Blumgart and Weiss, 1927). They injected radium C into an antecubital vein and recorded the time lapsing before its appearance in the corresponding arterial segment of the other arm to which a suitable detecting device of the Geiger counter type was applied. The elaboration of this method and its extensive clinical application in health and disease form the basis of a series of outstanding publications by Blumgart and Weiss (1927, 1928) and of a later review by Blumgart (1931). The recording of circulation time by this method however, though safe and apparently accurate, necessitated expensive apparatus and for this and other obvious reasons was impracticable outside research institutions. Accordingly Weiss, Robb and Blumgart (1929) from their consideration of the known effect of histamine on small vessels decided that this drug might serve for the estimation of circulation time in a simple way. They injected histamine intravenously in the dosage of 0.001 mg. per kilogram body weight in 1/5000 or 1/10,000 solution. The time of arrival of the drug in the small vessels of the face was recognizable by visible flushing of the skin; this in turn involved more distant parts. It was possible then to measure arm to face, arm to hand and arm to foot times with an accuracy, they claimed, not much less than with
radium C.

Of all methods so far mentioned the determination of the end point is independent of the cooperation of the patient. It has long been known that the intravenous injection of calcium chloride is sometimes followed by a warm glow in the throat, tongue and mouth. On the strength of this simple pharmacological fact the intravenous injection of this drug came to be used for the determination of circulation time from the site of injection to the tongue (Hirschohn and Mandel, 1922; Kahler, 1930). This, in contrast to the previous "objective" methods, implies a subjective end point and demands the attentive co-operation of the patient. The almost unending diversification of technique since the popularisation of circulation time recording as a clinical test by Blumgart and Weiss (1927, 1928) has largely been concerned with such subjective end points. The basis of all remains the injection of a foreign substance into a vein and the detection of its arrival at a particular point in the vascular pathway. Variation lies in the substance injected and, consequently, in the end organ(s) specifically stimulated by it to the extent of being experienced in consciousness. In this way circulation times over different segments can be measured. The ideal is a substance which, when injected intravenously, is
<table>
<thead>
<tr>
<th>Test Substance</th>
<th>Mode of Administration</th>
<th>Site of Administration (a)</th>
<th>Circulation time calculated from</th>
<th>End Point at (b)</th>
<th>Circulation time over segment a-b Range in seconds*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radium C.</td>
<td>Intravenous injection</td>
<td>Arm (antecubital vein)</td>
<td>Beginning of injection</td>
<td>Other arm (brachial artery)</td>
<td>12 - 24</td>
<td>Blumgart and Weiss (1927)</td>
</tr>
<tr>
<td>Histamine</td>
<td></td>
<td></td>
<td></td>
<td>Right heart face</td>
<td>2 - 14</td>
<td>Blumgart and Weiss (1927)</td>
</tr>
<tr>
<td>Calcium Chloride</td>
<td></td>
<td></td>
<td></td>
<td>Tongue</td>
<td>13 - 30</td>
<td>Weiss, Robb and Blumgart (1929)</td>
</tr>
<tr>
<td>Decholin</td>
<td></td>
<td></td>
<td></td>
<td>Tongue</td>
<td>9 - 15</td>
<td>Kahler (1929)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tongue</td>
<td>9 - 14</td>
<td>Winternitz, Deutsch and Brüll (1928)</td>
</tr>
<tr>
<td>Saccharin</td>
<td></td>
<td></td>
<td></td>
<td>End of injection</td>
<td>10 - 16</td>
<td>Tarr, Oppenheimer and Sager (1933)</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
<td>Carotid sinus</td>
<td>9.5 - 16</td>
<td>Wood (1926)</td>
</tr>
<tr>
<td>Sodium cyanide</td>
<td></td>
<td></td>
<td></td>
<td>Lung</td>
<td>8 - 21</td>
<td>Nylin (1941): Malmström and Nylin (1941)</td>
</tr>
<tr>
<td>Ether</td>
<td></td>
<td></td>
<td></td>
<td>Lung</td>
<td>9 - 15.75</td>
<td>Fishberg, Hitzig and King (1933)</td>
</tr>
<tr>
<td>Paraldehyde</td>
<td></td>
<td></td>
<td></td>
<td>Lung</td>
<td>8 - 16</td>
<td>Hitzig (1934)</td>
</tr>
<tr>
<td>Paraldehyde and ether combined</td>
<td>5 seconds after start of injection.</td>
<td></td>
<td></td>
<td>Lung</td>
<td>3.5 - 6</td>
<td>Caudel and Rabinowitz (1937)</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td></td>
<td></td>
<td></td>
<td>Lung</td>
<td>9 - 15</td>
<td>Fishberg, Hitzig and King (1933)</td>
</tr>
<tr>
<td>Macosil</td>
<td></td>
<td></td>
<td></td>
<td>Lung</td>
<td>8 - 18.5</td>
<td>Robb and Weiss (1924)</td>
</tr>
<tr>
<td>Diocrist</td>
<td></td>
<td></td>
<td></td>
<td>Left ventricle</td>
<td>7 - 22</td>
<td>Hitzig (1934)</td>
</tr>
<tr>
<td>Magnesium</td>
<td></td>
<td></td>
<td></td>
<td>Tongue</td>
<td>5 - 23</td>
<td>Blau (1940, 1942)</td>
</tr>
<tr>
<td>Sulphate</td>
<td></td>
<td></td>
<td></td>
<td>Conjugativa</td>
<td>3 - 9.5</td>
<td>Baer (1940, 1942)</td>
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<tr>
<td>Carbon dioxide</td>
<td>Inhalation</td>
<td>Lung</td>
<td>Beginning of inspiration</td>
<td>Tongue</td>
<td>5 - 10</td>
<td>Lange and Boyd (1942)</td>
</tr>
<tr>
<td>Fluorescin (U.V.)</td>
<td>Intravenous injection</td>
<td>Arm</td>
<td>Beginning of injection</td>
<td>Medulla</td>
<td>5 - 10</td>
<td>Piccione and Boyd (1941)</td>
</tr>
<tr>
<td>Lobeline</td>
<td></td>
<td></td>
<td></td>
<td>Lip</td>
<td>7 - 17.6</td>
<td>Bernstein and Simkins (1939)</td>
</tr>
<tr>
<td>Thorium X</td>
<td></td>
<td></td>
<td></td>
<td>Carotid sinus</td>
<td>5 - 12</td>
<td>Gubner, Schnur and Crawford (1939)</td>
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<tr>
<td>Papaverine</td>
<td></td>
<td></td>
<td></td>
<td>Medulla</td>
<td>12 - 20</td>
<td>Fishback (1941)</td>
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<td>Methylene blue (photo-electric)</td>
<td></td>
<td></td>
<td></td>
<td>Tongue</td>
<td>15.4 - 27.0</td>
<td>Elke and Solarz (1942)</td>
</tr>
<tr>
<td>Ammonaphylline</td>
<td></td>
<td></td>
<td></td>
<td>Tongue</td>
<td>7 - 21.6</td>
<td>Jablons and Cohen (1943)</td>
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<tr>
<td>Thiamine</td>
<td></td>
<td></td>
<td></td>
<td>Tongue</td>
<td>7 - 20.4</td>
<td>Koster and Sarroff (1943)</td>
</tr>
<tr>
<td>Nitrogen (oximetric)</td>
<td>Inhalation</td>
<td>Lung</td>
<td>Beginning of deep inspiration</td>
<td>Medulla</td>
<td>5 - 12</td>
<td>Ruskin and Rockwell (1945)</td>
</tr>
<tr>
<td>'Tagged' red corpuscles (radio-active phosphorus)</td>
<td>Intravenous injection</td>
<td>Arm</td>
<td>End of Injection</td>
<td>Tongue</td>
<td>8.7 - 10.7</td>
<td>Swenson (1946)</td>
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<td>Riboflavin and fluorescin</td>
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<td></td>
<td>Beginning of Injection</td>
<td>Tongue</td>
<td>4.1 - 7.0</td>
<td>Wexler, Whittenberger and Himelfarb (1946)</td>
</tr>
</tbody>
</table>

* This column is an accurate reproduction of the figures provided by the authors concerned, hence the erratic appearance of the decimal notation.

** In Manchester and Loub's recordings the stop watch is first set going when the hand registers 5 seconds after the injection is started. The watch is stopped when the end point is reached and the circulatory time calculated by subtracting 5 seconds from the total time recorded. The purpose of this elaboration is not clear.

*** The composition of Macosil is as follows: 42 grams of magnesium sulphate, 16 grams of calcium gluconate, 0.9 grams of sodium chloride and 1.0 mg. of copper sulphate, in 100 cc. of distilled water.
harmless and registers unfailingly a delicate specificity of end point. Numerous drugs have in their time been credited with these properties and used extensively for recording circulation times (Table 11). Examples are decholin which produces a bitter taste in the mouth (Winternitz, Deutsch and Brüll, 1931), saccharin which produces a sweet taste (Fishberg, Hitzig and King, 1933) and macasol* which causes a sensation of warmth in the part traversed (Kvale and Allen, 1939); ether (Hitzig, 1934) and paraldehyde (Caudel, 1937), both recognizable by their characteristic smell. A number of other substances (in addition to some already mentioned) that, by reason of their physico-chemical properties, determine an end point discernable to the observer have also been used. Such are sodium cyanide (Robb and Weiss, 1933), lobeline (Piccione and Boyd, 1941), papavarine (Mlek and Solarz, 1942), and aminophylline (Koster and Sarroff, 1943) which, acting on the respiratory centre or chemo-receptors, cause an involuntary change in respiration; "tracer" substances which can be detected in the circulation by reason of their fluorescence (Lange and Boyd, 1942) or radioactivity.

* Macasol, originally introduced by Spier, Wright and Saylor (1936), is a solution of 42 grams magnesium sulphate, 16 grams calcium gluconate, 0.9 gram sodium chloride and 1 mg. copper sulphate in 100 cc. distilled water.
(Nylin and Malm, 1944). The immediate gaseous change in the circulating blood consequent on the inhalation of nitrogen can be registered in the systemic capillaries with the oximeter (Wexler, Whittenberger and Himmelfarb, 1946). This instrument permits of direct measurements of circulation time over particular vascular segments not otherwise accessible.

Critical evaluation of circulation time as an index of the velocity of blood flow. The tests of circulation time used in this investigation suffer from the disadvantage that the end points are determined subjectively and, as such, are variable. It is believed however that if patience and care are exercised in explaining to the patient all the implications of the test the end points are sharply defined. Decholin is very bitter to the taste and no ordinary individual who has experienced that taste can have much difficulty in indentifying it. The odour of ether is familiar to most; the exception can be made familiar without the necessity of an injection. Usually the patient has no doubt about the reality of the stimulus and the truth of his affirmation is reflected in the exuberance of his response and in the expression on his face. Failure to register an end point has been observed but among none of the subjects now under consideration. With the quantity of both drugs used the end points are
likely to be equivocal only when, by natural endowment or disease, the patient is unable to apply the limited mental effort required of him. It is superfluous to state that there is an individual variation in the delicacy of taste and smell perception but this is unlikely, with the exception stated, to extend to so gross a stimulus.

The ether time includes the interval involved in the movement of the gas from the pulmonary alveoli to the olfactory nerve endings, and its duration might be expected to vary according to the phase of respiration in which the ether arrived in the alveoli. Of this Hitzig (1934) wrote that the rate of diffusion of ether in a gaseous mixture is so great "that the time required for its ascent to the nasopharynx is negligible compared to the actual circulation time"; he was unable to adduce any evidence of its variation with the phase of breathing.

Nylin (1945), who has used decholin extensively, found close agreement between circulation times as measured by this drug and by injection of red blood corpuscles labelled with radioactive phosphorous. Against the reputedly greater accuracy of methods involving on objective end point is the fact that the normal range reported by Blungart and Weiss (1927) for arm to heart time measured with radium C exceeds, proportionally, that recorded for any segment of the
circulation by any other method. But no detailed information is given concerning the distribution within that range, and there are many reasons for variation in the circulation time of the short peripheral venous segment.

In his review of the subject Blumgart (1931) defined circulation time as "the interval of time necessary for the fastest particle of a foreign substance to traverse the shortest available path between the point of injection and the point of detection." This definition is true so long as the time defined is measurable, for there is no reason why the term should not be restricted to maximum velocity. But it is not measurable by many, and probably by none, of the numerous tests of circulation time in use at the present time. Where the end point is subjectively determined, as with decholin and (in most cases) ether, not only the fastest particle but a minimum aggregate of particles per unit of time, varying with the individual and with the drug used, is required to stimulate the nerve endings concerned to the extent of being registered in consciousness (Ruskin and Rockwell, 1945).

Blumgart and Weiss (1927) observed that increasing the quantity of radium used in the injection did not affect the circulation time. They did not, however, investigate the effect of reducing the dose
beyond the standard adopted. Winternitz, Deutsch and Brüll (1931), using histamine, noted that increasing from approximately 1 cc. to 5 cc. the volume in which the same weight of drug was injected reduced the circulation time and gave less variable results. Robb and Weiss (1933) found that by injecting small quantities of sodium cyanide circulation times were recorded in excess of those obtained with larger quantities of the drug. Tarr, Oppenheimer and Sager (1933), though normally injecting 5 cc. (20 per cent) decholin, found that they could get a definite end point in some but not in all with as little as 3 cc. They wrote that "in general the faster the circulation time the less substance is needed to produce the taste." Hitzig (1935) observed that in reducing the amount of ether injected for measuring arm to lung time from 0.33 cc. to 0.15 cc. "not only was the end point with the smaller dose less defined but the circulation time showed a prolongation of from 1.5 to 3 seconds". He also noted that both "the delay and the lessened acuity of the end point were even more marked" when to the smaller dose was added 3 cc. of saline. He attributed the prolonged circulation time to the longer time implied in the injection of a larger volume, to the less ready volatilisation of the diluted ether, and to the lower pressure gradient of the ether in the alveoli when the smaller quantity
was used. To prove that this pressure gradient was adequate with his standard dose of 0.33 cc. he injected 0.66 cc. on occasions and found no significant diminution in arm to lung time. Kvale and Allen (1939), using macasol as a test substance, found that "blanks" (i.e. absence of recognisable end point) were much more frequent when the foot was used as detector point compared with the hand. They also noted that "blanks" were more frequent on cold days than on warm and that by warming the skin artificially they increased the number of recorded end points - and diminished the circulation time. Elek and Solarz (1942), by increasing the dose of papavarine injected from 32 to 52 mg., reduced the estimated circulation time from 25 to 21 seconds, a finding which they dismissed as of no significance. The validity of these variations can very simply be appreciated by measuring circulation time with, for example, decholin. Beginning with 1 gram in a volume of 5 cc., arm to tongue time is measured daily with successively smaller quantities of the drug in the same volume. The circulation time as recorded will remain constant until a certain minimum quantity of decholin is used and will then become progressively longer until eventually no end point is registered. A similar prolongation of circulation time can be produced by decreasing, within limits, the ratio of
volume to weight, the latter remaining constant.

The significance of these variations in estimated circulation time is obvious; their control is imperative if the measurement of circulation time is to have any accuracy and its clinical application any value. From their experiments with several of the common test substances Ruskin and Rockwell (1945) concluded that there is a logarithmic variation of circulation time and dosage of drug used. They suggest that there is an optimum dose for each drug, varying with the individual, and that suboptimal doses cause either a prolongation of circulation time as measured or fail to produce an end point, but that increasing the dose beyond a certain (optimum) level fails to cause appreciable shortening of the circulation time. The equivalent of a suboptimal dose, they state, is produced by dilution which may result from "slowing of the circulation as in congestive failure" or from a greater distance to the point of detection. The same authors, commenting on their observation that with a constant dose of drug increasing the volume in which it is injected reduces the recorded circulation time, remark that an analogous effect would be produced by shortening the duration of the injection. Most investigators have stressed the desirability of rapid injection and to this end used large needles, so that Hitzig (1934) was able to claim as one of the advantages of ether the brief time (less than 0.5 second) involved in the actual injection. Large
volumes (of injection) introduce conflicting influences - the greater volume itself conducing to a shortening of the circulation time and the necessarily longer duration of injection tending to prolong it. The effort to reduce the injection time to a minimum brings in another factor which Ruskin and Rocwell (1945) describe as significant in lessening the recorded circulation time, namely the pressure applied to the solution as it leaves the syringe.

Blumgart (1931) in his definition of circulation time assumed that every particle in the circulating blood moves with equal velocity. This is not the case even in the simplest physical arrangement of fluid in motion for the articles in the central or axial stream move forward more rapidly than those at the periphery (von Kries, 1887, Tigerstedt, 1903). Microscopical observation of blood flow in small vessels reveals similarly, a faster motion of the corpuscles in the axial stream than in the peripheral layers (Wiggers, 1940). In such a streamlined flow only a mean of velocities, which diminish from the centre to the periphery, could be reasonably representative of the velocity of blood flow as a whole. The turbulence that is presumed to underlie the bruit of anaemia and the murmur of stenosing lesions (Wiggers, 1940) further increases the difficulty, in those cases, of calculating an average velocity of blood flow.
Holt, Reshkind, Bernstein and Greisen (1946) studied the dynamics of blood flow in anaesthetised dogs by injecting a dye into the right auricle and observing the arrival and concentration of dye particles in systemic arterial blood (e.g. femoral). They noted that "when the dye injection is started the dye in the axial stream moves fastest and reaches the artery in a certain time ("appearance time"). A short time later more dye reaches the artery, for not only the fastest moving (axial stream) dye reaches the artery but some of the slower moving particles also. Finally the slowest moving particles of dye reach the artery as well as the fastest moving particles and we get a dye concentration in the arterial blood that remains constant for a few seconds". They equate with Blumgart's circulation time what they term "appearance time", which reflects the velocity of the axial stream or Blumgart's fastest particle. They define "average circulation time" as the time taken by "a dye particle moving with the average velocity of all dye particles" in passing from the site of injection to the point of detection. They determine this "average circulation time" graphically from a plasma dye concentration - time curve.

Nylin and Malmström (1942), measuring arm to tongue time with decholin in 48 healthy persons,
found that the persistence of the decholin taste (measured from the first appreciation of the sensation to its ultimate disappearance) varied from 7 to 24 seconds, (mean 12.8 seconds, s.d. 4.0). They found also that the time over which the taste of decholin persisted was prolonged in the presence of enlargement of the heart, with or without congestive failure, but that its correlation with heart volume was considerably less than was that of the arm to tongue time measured to either the beginning or the end of the taste sensation.

The end point of the "average circulation time" (Holt et al., 1946) lies somewhere in the taste persistence period (Nylin et al., 1942). Although such an "average circulation time", if accurately calculable, is undoubtedly a better index of average velocity of blood flow than is the circulation time measured to the beginning of the specific sensation there is no evidence to suggest that it is a better index of the efficiency, as distinct from the velocity, of the circulation, nor that it reflects change in the velocity of the circulation before the other.

The segmental circulation times measured by Blumgart and Weiss (1927, 1928), using radium C, were the arm to heart and arm to arm times. They considered that the difference between these two represented pulmonary circulation time and, in doing so, presumed that the velocity of blood flow through the heart and
major arteries is so rapid as to be inconsequential in varying the circulation time. They argued that with a heart rate as slow as 60 and the test substance arriving in the right auricle immediately after the auriculo-ventricular valves had closed the maximum prolongation of circulation time so produced would be one second; in the remote chance of the injected radium arriving successively in the left auricle at the corresponding phase in the cardiac cycle the result would be the greatest possible prolongation of circulation time that the heart could produce in any circumstances, namely 2 seconds. They remarked that prolongation of circulation time almost invariably implies congestive heart failure. Every investigator of circulation time who succeeded them has reported the association between congestive failure and prolonged circulation time.

Hitzig (1934) emphasised that ether was so volatile at blood temperature that when a small quantity was injected into a systemic vein sufficient was volatilised on its arrival in the pulmonary capillaries during the first circuit of blood to make its odour invariably perceptible. He described the segment of circulation traversed by the ether, i.e. from the antecubital vein to the pulmonary capillaries, as "the right heart unit" and claimed that arm to lung time, thus measured, was "an index of the functional capacity of the right heart"; in
the same way lung to tongue time, or the difference between saccharin and ether times, reflected the functional efficiency of the left ventricle. The vascular pathway represented by the lung to tongue time he called "the left heart unit". The arm to tongue time, estimated with saccharin (Fishberg, 1933) and found to agree closely with decholin time, was regarded as being dependent on the efficiency of both ventricles and therefore liable to be prolonged in failure of either. Pure left ventricular failure was associated with pulmonary congestion, prolonged lung to tongue time and normal arm to lung time; right ventricular failure with a high systemic venous pressure, prolonged arm to lung time, and a normal lung to tongue time. Hitzig (1934) offered these observations on segmental circulation times as "convincing support for the backward failure theory" of heart failure in that the initial retardation of blood flow occurs in that part of the circulation immediately behind the ventricle that is failing. This conception of the dynamics of congestive heart failure is still acceptable to White (1945), and Manchester and Loube (1946) preface their report on an investigation into the circulation time in pregnancy with - "In isolated left ventricular failure when the physical signs may be meagre the only evidence of its presence may be a prolonged arm to tongue and lung to tongue time. In like manner, it is possible to recognise the imminence
or presence of right heart failure by the prolonged arm to tongue and arm to lung time, even before the venous pressure is raised".

In 1941 however David and Bouvrain, for the first time, reported a relationship between the velocity of blood flow and heart size. A short time later Malmstrom and Nylin (1942) observed a "decided relation" between the circulation time and heart volume "in patients with compensated cardio-vascular disease". Heart volume was calculated from two orthodiagrams taken simultaneously in two projections at right angles by a method previously described by Rohrer (1916), and by Liljestrand, Lysholm, Nylin and Zacheisson (1939). Nylin (1943) suggested that under both physiological and pathological conditions "the heart is subject to considerable sudden volume changes....(which) are due to variations in the amount of residual blood", and that the prolongation of circulation time "is largely an indication of the amount of residual blood". Meneely and Kaltreider (1943) reported that of 15 patients with advanced congestive heart failure in 8 who were examined radiologically there was a linear relationship between the logarithm of the circulation time and the heart size as expressed by the cardio-thoracic ratio. Gernandt and Nylin (1946) concluded that "in both compensated and decompensated heart disease there is a statistically verified correlation between the heart volume, i.e. the
amount of residual blood, and the circulation time . . . .", and also that "... above all, the circulation time depends on the amount of residual blood in the heart and only to a slight extent on the degree of decompensation, i.e. of congestion". Their conclusions are less convincing to this reader than they obviously are to the authors themselves, and not only because a "statistically verified correlation" implies, of necessity, in the way of causation - nothing. Further according to Nylin (1943), "residual blood is the blood remaining in the heart cavities after completion of systole; (and)... when the heart contains a large amount of residual blood it must take a considerably longer time for the heart to empty its blood, including the decholin, than for a heart of normal size with a small amount of residual blood". Therefore, he concludes, the circulation time is prolonged.

The concept of "residual blood" would appear to be quite superfluous. The heart dilates because the myocardium is diseased or for some other reason fails adequately to eject its contents during systole. In these circumstances, irrespective of whether the heart disease is "compensated" or "decompensated" (which appears to be the equivalent of stating that there is no peripheral oedema or that there is), circulation time is prolonged, certainly because of delay in complete ejection of the drug but also because of its
greater dilution in the dilated heart which is in fact the reason for its delayed ejection. Longer persistence of the decholin taste, flattening and shift to the right of the red cell dilution curve (Nylin, 1945) occur for the same reason. All is secondary to a malfunctioning myocardium, including the fact that there is more "residual blood". The latter has least claim to special recognition. To emphasise its importance in the prolongation of circulation time is to minimise the importance of the myocardium in the genesis of heart failure, and there are few who would agree that that is a reasonable thing to do.

Nathanson and Elek (1947) on the same subject found in "70 compensated cardiac patients with cardiac enlargement", whose circulation time they estimated with macasol, "a rough correlation" between the degree of cardiac enlargement and circulation time. They concluded that "a prolonged circulation time does not necessarily signify an actual reduction in the velocity of the blood but may be due to an improper mixing and a dilution of the test substance in the increased residual blood of the dilated heart". How it can be said of the test substance, under these circumstances, that it is both improperly mixed and diluted is not understood. Nor in fact is any of the reasoning that underlies the words quoted. That the heart is the pump of the circulation does not detract from the fact
that it is also part of the containing system of the circulating blood. In any system, however simple or complex, containing fluid in motion a local increase in cross-sectional area must tend to a reduction in the velocity of the fluid in that part and therefore in the average velocity in the whole circuit - irrespective of all other variables. Theoretically such an effect should be produced by an aneurysm; that it is has been demonstrated, but a sufficiency of material has not been available to make the proof unequivocal. The association of a prolonged circulation time with heart disease in the absence of "decompensation" has been remarked upon from time to time by many observers (Blumgart et al. 1927; Baer and Slipakoff, 1938; Wall, 1939; Neurath, 1937; Hussey, Neurath, Wallace and Sullivan, 1942) but, with little exception, they were eager to imply that significant prolongation meant the presence of heart failure. The apparent inconsistency was due to too zealous application of the principle of "decompensation" and too little attention to the functional capacity of the myocardium as distinct from the size of the heart. Blumgart and Weiss (1927) suggested that the slowing of the circulation in these circumstances was a "back-pressure" effect on the pulmonary circulation. Baer and Slipakoff (1938) interpreted it as the onset of congestive failure. Most offered no explanation.
Despite this hesitancy to accept a prolonged circulation time in "compensated" heart disease it had previously been shown, experimentally and clinically, that in the evolution of congestive heart failure slowing of blood flow precedes recognizable increase in peripheral venous pressure (Starling, 1920; Blumgart, 1931; Hitzig, 1934, 1935; Fishberg et al., 1933; Fishberg, 1937; Caudel and Rabinowitch, 1937; Manchester and Loube, 1946). That there is in the presence of congestive failure a retardation or, in the advanced stage, actual reversal of capillary circulation has been proved by direct micro-observation (Wiggers, 1940). But these facts apart, the assertion that the locus of the prolongation of circulation time is, under certain circumstances, within the heart chambers (Nylin et al. 1943, 1946; Nathanson et al. 1947) does not lessen its significance nor alter its interpretation. It was never intended that the cavities of the heart should be excluded from the calculation of circulation time. Blumgart and Weiss (1927) included an estimate of circulation time through the heart in their calculation of "actual pulmonary circulation time" but did not take account of its potential variation. Vierordt (1858), who himself studied the velocity of blood flow in a variety of animals and advanced the technique of doing so, had pointed out that the time taken by a dye (which he used as test substance) to
pass through the heart must vary according to the phase of the cardiac cycle in which it arrives there, and that the estimated circulation time must vary accordingly. He argued further that in proportion as the heart fails to empty itself completely during systole so the circulation time as estimated will be shorter than the true circulation time for the reason that the dye will mix in the heart with blood that had traversed the same vascular pathway as itself but in advance of it, and will be ejected with that blood during the succeeding ventricular systole. The injected dye (and blood) in Vierordt's view moved forward as a column and, obviously, to continue his argument on incomplete emptying, the circulation time would be longer if the dye happened to arrive in the ventricle at the earliest phase of diastole and thus be ejected with blood arriving later in time. This concept does not differ fundamentally from the modern version of prolongation of circulation time by "improper mixing", dilution, and "residual blood" (Nathanson et al. 1947). Unfortunately Vierordt's concern was with establishing a source of error in recorded circulation times and it was his misfortune to limit his consideration in this instance to variations within the confines of a single cardiac cycle.

Notwithstanding valid criticism measurement of circulation time still serves a useful purpose in providing an objective record of circulatory efficiency
and compares favourably with other biological tests. That the "range of normal values overlaps the abnormal values" (Meneely and Chesnut, 1947) is not valid criticism. It is inevitable in the natural order of things, irrespective of what is being measured. The criticism is not valid even "in the very cases where the differential significance of the test would be most important" (Meneely et al. 1947). As a single observation the test has its greatest usefulness in the differential diagnosis of paroxysmal dyspnoea. Where this is caused by left ventricular failure there is no doubt about the prolongation of lung to tongue or arm to tongue times (Fishberg et al., 1933; Plotz, 1939); other causes are not of themselves associated with any increase in circulation time. But in the individual patient the recording of circulation time gives maximum information when done at intervals during the course of his illness. As such it is probably the most sensitive index of change in cario-vascular efficiency. In the presence of congestive heart failure of any grade the circulation time is invariably lengthened relative to the "normal" for that particular patient.

Almost all investigators have stressed the near equality of duplicate records in the same individual in health and under standard conditions (Blumgart, et al., 1931; Tarr et al., 1933; Fishberg (1933; Hitzig, 1934),
## TABLE III

**DUPLICATE RECORDS AT BRIEF INTERVALS OF THIAMINE (ARM TO TONGUE) CIRCULATION TIME IN "50 NORMAL SUBJECTS", (AFTER SWENSON (1946))**

<table>
<thead>
<tr>
<th>NUMBER OF PATIENTS</th>
<th>AGE GROUP</th>
<th>FIRST</th>
<th>DUPLICATE</th>
<th>&quot;DEVIATIONS IN SECONDS&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>16 - 30</td>
<td>8.7</td>
<td>9.7</td>
<td>-2, +4</td>
</tr>
<tr>
<td>16</td>
<td>30 - 40</td>
<td>10.1</td>
<td>10.5</td>
<td>+4</td>
</tr>
<tr>
<td>18</td>
<td>40 -</td>
<td>10.7</td>
<td>10.7</td>
<td>+3.3</td>
</tr>
</tbody>
</table>

* The second recording was made as soon as the taste sensation following the first injection ceased to be perceptible, the needle remaining in the vein the while.
although not giving their figures in detail. Ruskin and Rockwell (1945) have chosen to question the constancy of such duplicate measurements in methods involving a subjective end point. They suggested that "the sensory nerves of the tongue and throat are apparently depressed in some patients by smoking, old age and previous strong tastes". Such a raised threshold of stimulation produces the same effect as a suboptimal dose and may, they considered, occur when injection of the drug is repeated within several minutes of its previous use. Swenson (1946), using thiamine, calculated circulation time as the average of two recordings separated by a brief interval of this kind and produced figures for the mean first and second measurements in three groups of 16, 16 and 18 "normal" individuals (Table 111). These figures are compatible with a rising threshold of stimulation but the information available permits no statement of criticism beyond this. Nor on this subject are there any figures available that substantiate or refute the reasonable criticism of Ruskin and Rockwell (1945).

The duplicate (and triplicate) check records in the present investigation were made at 24 hour intervals and no apparent constant variation was found to exist in these circumstances in 50 healthy controls. It was part of the design of the investigation however that the first recording of each circulation time should be regarded only as serving to familiarise the subject
with the implications of the test. Accordingly the first records obtained from all controls and all patients during the period of this investigation were discarded, irrespective of their agreement with records made 24 hours later and irrespective of whether the individual had previously been investigated or not. There are two exceptions to this statement - inevitable because two patients died within 24 hours of their admission to hospital (Cases 55 and 62., Table IX, opposite p. 84). The initial recording in these is included in the results to be presented, and since this is so it is pertinent to mention that in one of the two all investigations were repeated before he died (and the results also included). He moreover had previously been hospitalised and investigated in the same way. This patient will subsequently be referred to in detail. The second patient was under investigation for the first time and in his case the observations were not repeated.

Among the numerous drugs that have been used in the study of circulation time (Table II) there is undoubtedly, under the conditions of the test, a wide
variation in the acuity of the end point. The metabolic level of the individual, his posture and emotional state, the environmental temperature and many other factors are potential influences in this as in other biological tests, but Ruskin and Rockwell's comprehensive assessment of absolute and relative inadequacy of dosage as a source of error is likely to include the cause of most variations under standard conditions. Few observers, unfortunately, provide the figures necessary for an appreciation of the frequency distribution of circulation times, and many record their mean and range from a large number of observations on a small number of individuals. The result is that comparison is not always justifiable. With all test substances however the recorded range of circulation time in normal individuals is fairly wide. A representative range of arm to tongue time by decholin is 10-16 seconds (Tarr et al., 1933), by soluble gluside 9-16 seconds (Fishberg et al., 1933).
TABLE IV

REPORTED DISTRIBUTION OF MACASOL

CIRCULATION TIMES (MODIFIED FROM MENEELY AND SEGALOFF (1947))

<table>
<thead>
<tr>
<th>REFERENCE</th>
<th>SUBJECTS</th>
<th>STATISTIC</th>
<th>TONGUE</th>
<th>PERINEUM</th>
<th>HAND()</th>
<th>FOOT()</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spier, Wright and Saylor (1936)</td>
<td>&quot;35 normal subjects, 40 tests.&quot;</td>
<td>&quot;Resting&quot; mean</td>
<td>14.6</td>
<td>21.5</td>
<td>26.2</td>
<td>27.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&quot;Average deviation&quot;</td>
<td>±3.23</td>
<td>±4.59</td>
<td>±5.26</td>
<td>±7.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range.</td>
<td>7-22</td>
<td>12-32</td>
<td>11-43</td>
<td>10-48</td>
</tr>
<tr>
<td>Kvale and Allen (1939)</td>
<td>&quot;13 normal subjects, 73 tests.&quot;</td>
<td>&quot;Basal&quot; mean</td>
<td>13.76</td>
<td>21.22</td>
<td>23.6</td>
<td>34.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Standard deviation</td>
<td>±2.65</td>
<td>±5.14</td>
<td>±5.74</td>
<td>±9.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range.</td>
<td>5-24</td>
<td>10-34</td>
<td>10-39</td>
<td>15-39</td>
</tr>
<tr>
<td></td>
<td>&quot;51 normal subjects, 96 tests.&quot;</td>
<td>&quot;Resting&quot; mean</td>
<td>13.7</td>
<td>21.0</td>
<td>23.5</td>
<td>32.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Standard deviation</td>
<td>±3.52</td>
<td>±5.52</td>
<td>±6.04</td>
<td>±9.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range.</td>
<td>5-29</td>
<td>10-44</td>
<td>10-44</td>
<td>20-69</td>
</tr>
</tbody>
</table>

\(\) Average of right and left hand and right and left foot.

\(\)\(\) Macasol is a solution of 42 grams magnesium sulphate, 16 grams calcium gluconate, 0.9 grams sodium chloride and 1.0 mg. copper sulphate in 100 cc. distilled water.
saccharine 9-15.75 seconds (Fishberg et al., 1933)
calcium gluconate 8-16.5 seconds (Baer, 1939),
magnesium sulphate 7-17.8 seconds (Bernstein and Simkins, 1939), macasol 5-29 seconds (Kvale and Allen, 1939), thiamine 5-12 seconds (Ruskin et al., 1945).
The range as recorded on all occasions with macasol is wider than with other drugs, which caused Kvale and Allen (1939) to suggest that the characteristic sensation of warmth that constitutes its end point does not necessarily correspond to the arrival of the drug at the site of stimulation, although the sensation is a consequence of its arrival. The range appears to increase as the point of detection becomes more distant from the heart (Table IV), e.g. macasol arm to tongue time is 5-29 seconds, arm to perineum 10-44 seconds, and arm to foot 20-69 seconds (Kvale and Allen, 1939). With drugs producing an end point by acting on the respiratory centre or chemo-receptors the range of circulation time has been reported as follows:— sodium cyanide 9-21 seconds (Robb and Weiss, 1933), aminophylline 7.1-20.4 seconds (Koster and Sarroff, 1943), papavarine 15.4-27 seconds (Flek and Solarz, 1942), and lobeline 5-12 seconds (Piccione and Boyd, 1941). Of arm to lung time Hitzig (1934) found with ether a range of 3.5-8 seconds, Caudel (1937) with paraldehyde 3-9.5 seconds, Baer (1940) with ether 3-9.5 seconds. The natural variation of arm to lung time as recorded by all techniques is,
so far as can be judged from the figures available, apparently greater proportionally than that of arm to tongue time. The short segment of circulation involved would of itself conduce to diminishing the time recorded. It is interesting that Blumgart and Weiss (1927, 1928) in their objective recording of circulation time with radium C found the peripheral venous (arm to heart) time more variable (2-14 seconds) than have other observers using so called "subjective" methods. They attributed the wide scatter of arm to heart time to "the great variability of volume of blood flow in the arm" - which is not very revealing. Of the many influences potentially operative in varying circulation time the volatilisation and diffusion of the gas involved in estimating arm to lung time creates a variable peculiar to this segment alone. None the less, with any single reliable drug injected in optimum dosage by one observer under standard conditions results are strictly comparable. They still are comparable under the same conditions when different observers use the same drug or even a limited number of different drugs (Table 11). Thus arm to tongue time estimated with decholin (Tarr et al., 1933; Wood, 1936), saccharin (Fishberg et al., 1933; Baer et al., 1938), and calcium gluconate (Goldberg, 1936; Baer, 1939) correspond closely, as do arm to lung times with ether (Hitzig, 1934, 1935; Baer, 1940) and paraldehyde (Candel, 1937). The more recently introduced "objective" methods involving the injection of fluorescent tracer substances (Lange and
Boyd, 1942; Hubbard, Preston and Ross, 1942; Winsor, Adolph, Ralston and Leiby, 1947) or red blood corpuscles labelled with radioactive phosphorus (Nylin and Malm, 1944) might be expected to yield a greater accuracy but already Nylin (1945) has stressed the close correspondence between arm to tongue times as measured with radioactive phosphorus and with dec- holin. The oximeter (Wexler, Whittenberger and Himmelfarb, 1946) permits of direct recording of circulation time from the pulmonary to the systemic capillaries. This is likely to provide the most accurate assessment of velocity of blood flow over a particular segment of circulation of all methods yet in use.

Vierordt (1858) observed that in different animals the circulation time over corresponding anatomical pathways varies directly with the size of the animal and that, irrespective of size, the circulation time over a particular segment of circulation corresponds in time to a nearly constant number of heart beats. This is as would be expected for the distance traversed is shorter in the smaller animal and, generally, the smaller the animal the greater is the heart rate. The result is that the product of circulation time and heart rate is (approximately) constant in different animals. Blum- gart and Weiss (1927) suggested that circulation time in man becomes shorter as the ventricular rate increas- es, but only in pronounced tachycardia was this
TABLE V

REPORTED NORMAL RANGE\textsuperscript{x} OF CIRCULATION TIMES IN CHILDREN

<table>
<thead>
<tr>
<th>NUMBER OF CHILDREN INVESTIGATED</th>
<th>TEST SUBSTANCE</th>
<th>MODE OF ADMINISTRATION</th>
<th>SITE OF ADMINISTRATION ((a))</th>
<th>CIRCULATION TIME CALCULATED FROM (\text{END POINT} \at \text{(b)})</th>
<th>CIRCULATION TIME OVER SEGMENT (\text{a to b. RANGE, SECONDS})</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Saccharin</td>
<td>Intravenous Injection</td>
<td>Arm (antecubital vein)</td>
<td>Beginning of injection</td>
<td>Tongue 5.0 - 13.5</td>
<td>Averbuck and Samuel (1935)</td>
</tr>
<tr>
<td>5</td>
<td>Ether</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>Lung 2.5 - 5.5</td>
<td>Hitzig (1935)</td>
</tr>
<tr>
<td>?</td>
<td>Radioactive sodium</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>Other arm (brachial artery) 5.0 - 17.0</td>
<td>Hubbard, Preston and Ross (1942)</td>
</tr>
</tbody>
</table>

\textsuperscript{x} Data provided are inadequate for statistical analysis.
noticeable. They noted a tendency to shorter circulation times in children compared to adults and attributed this to the faster heart rate in the former. They inferred that the velocity of blood flow was actually greater in large individuals than in small but that, apart from this, the only association between circulation time and age was by way of change in heart rate accompanying the latter. They established an inverse relationship between circulation time and basal metabolic rate. Kvale and Allen (1939), though dealing with numbers too small to justify their conclusions, found that circulation time was diminished during the tachycardia produced by intravenous injection of 1 mg. of atropine; they noted a corresponding change during digestion (of an unnaturally large breakfast taken after a period of self-denial). The same authors affirmed that there is no difference between the circulation time recorded in the basal state and that after resting for a few minutes only. Averbuck and Samuel (1935) measured circulation time with saccharin in 100 children aged 8 to 16 and recorded a mean arm to tongue time of 8.6 seconds and a range of 5 to 13.5 seconds (Table V). They concluded from this analysis alone that the arm to tongue time in children is significantly less than in adults. Hitzig (1935) found in 5 children aged 7 to 11 short ether times which he interpreted in the same way. Swenson's (1946) mean figures of thiamine arm to tongue
time in various age groups show an apparent increase with age but their significance is not established. A quantitative relationship has been observed between respiration rate and both saccharin and ether times; rapid breathing was associated with a measurable shortening of circulation time (Fishberg, et al., 1933; Hitzig, 1934). Apart from these variations successive investigators have, like Blumgart and Weiss (1927), reported an absence of correlation in healthy adults between circulation time and age, sex, height, weight, surface area, vital capacity, pulse rate, arterial and venous pressures (Tarr et al., 1933; Fishberg, 1933; Fishberg et al., 1933; Hitzig, 1934; Baer, 1939, 1940; Spier et al., 1936; Wood, 1936, Meneely et al., 1947). A lessening of circulation time occurs during physical exertion and in the presence of a raised environmental or body temperature.

The observations to be recorded were not made under basal conditions but were made under standard conditions of all the variables referred to so far as these were controllable. The dosage of decholin and ether used is considered to have been not less than the optimum for these (Ruskin et al., 1945). The duration of injection of decholin did not on any occasion exceed 2.0 seconds nor of ether 0.5 seconds. Ventricular rates in all were in the range 60 to 100. The youngest age included is 16.


TABLE VI

FREQUENCY DISTRIBUTION OF CIRCULATION TIMES AND BRACHIAL VENOUS PRESSURE

IN 50 CONTROLS

<table>
<thead>
<tr>
<th>Time in Seconds</th>
<th>Frequency</th>
<th>Frequency</th>
<th>Frequency</th>
<th>Frequency</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm to tongue (decholin) (a)</td>
<td></td>
<td></td>
<td></td>
<td>Brachial venous pressure (v.p.) in mm. blood above sternal angle</td>
<td></td>
</tr>
<tr>
<td>Arm to lung (ether) (b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung to tongue (a - b)</td>
<td></td>
<td></td>
<td>Change in brachial v.p. in mm. blood caused by compression of abdomen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td>9</td>
<td>3</td>
<td>0-</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5-6</td>
<td>28</td>
<td>3</td>
<td>5-</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7-8</td>
<td>8</td>
<td>4</td>
<td>10-</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>9-10</td>
<td>1</td>
<td>8</td>
<td>15-</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>11-12</td>
<td>2</td>
<td>11</td>
<td>20-</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>13-14</td>
<td>2</td>
<td>14</td>
<td>25-</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>15-16</td>
<td>4</td>
<td>7</td>
<td>30-</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>17-18</td>
<td>6</td>
<td>1</td>
<td>35-</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>19-20</td>
<td>7</td>
<td></td>
<td>40-</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>21-22</td>
<td>15</td>
<td></td>
<td>45-</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>23-24</td>
<td>10</td>
<td></td>
<td>50-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>12.02</td>
<td>4.73</td>
<td>7.28</td>
<td>17.40</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>8.2 - 14.6</td>
<td>3.6 - 9.3</td>
<td>3.1 - 9.9</td>
<td>3.0 - 46.0</td>
<td></td>
</tr>
<tr>
<td>Standard deviation</td>
<td>1.57</td>
<td>1.19</td>
<td>1.72</td>
<td>9.03</td>
<td></td>
</tr>
<tr>
<td>Standard error of mean</td>
<td>0.22</td>
<td>0.17</td>
<td>0.24</td>
<td>1.28</td>
<td></td>
</tr>
<tr>
<td>Co-efficient of variation</td>
<td>13.10</td>
<td>25.09</td>
<td>23.63</td>
<td>51.90</td>
<td></td>
</tr>
</tbody>
</table>
RESULTS OF THIS INVESTIGATION

Controls. The frequency distribution of segmental circulation times and brachial venous pressure in 50 healthy controls of ages varying from 16 to 65 is shown in Table VI.

Reference has been made to the usually reported absence of correlation between circulation time and age, sex, height and weight and to the statistical limitations of the few reports that may differ in this respect. Generalisations have too frequently been made in the past from inadequate samples and it is accepted that the present series, though adequate for the purpose of control in this investigation, is not worthy of consideration from the point of view of assessing natural variation over the comprehensive range of age, surface area and limb length displayed by mankind.

Emphysema. Table VII represents a similar analysis of 50 recordings of corresponding circulation times and venous pressure in 40 patients with emphysema.

The reason for the smaller number in this group is that in striving to include only uncomplicated emphysema, the rejection rate was high. Although this principle of selection was retained its strict application was found to be impracticable; otherwise all, or nearly all, severe emphysema of middle age
# TABLE VII

CIRCULATION TIMES AND BRACHIAL VENOUS PRESSURE IN UNCOMPPLICATED EMPHYSEMA

<table>
<thead>
<tr>
<th>CASE NUMBER</th>
<th>PATIENT</th>
<th>ARM TO TONGUE TIME IN SECONDS</th>
<th>ARM TO LUNG TIME IN SECONDS</th>
<th>LUNG TO TONGUE TIME IN SECONDS</th>
<th>BRACHIAL VENOUS PRESSURE (V.P.) IN MM. BLOOD ABOVE STERNAL ANGLE</th>
<th>CHANGE IN BRACHIAL V.P. CAUSED BY COMPRESSION OF ABDOMEN IN MM. BLOOD</th>
<th>PERSISTENT OEDEMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T.R.</td>
<td>10.0</td>
<td>4.1</td>
<td>5.9</td>
<td>65</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>J.K.</td>
<td>10.7</td>
<td>5.5</td>
<td>5.2</td>
<td>124</td>
<td>+ 2</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>G.F.</td>
<td>12.2</td>
<td>5.6</td>
<td>6.7</td>
<td>60</td>
<td>+ 2</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>M.W.</td>
<td>10.8</td>
<td>4.0</td>
<td>6.6</td>
<td>42</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>M.T.</td>
<td>11.4</td>
<td>5.9</td>
<td>5.5</td>
<td>53</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>6</td>
<td>E.C.</td>
<td>11.0</td>
<td>4.8</td>
<td>6.2</td>
<td>56</td>
<td>- 2</td>
<td>---</td>
</tr>
<tr>
<td>7</td>
<td>A.S.</td>
<td>7.3</td>
<td>3.7</td>
<td>3.6</td>
<td>25</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>8</td>
<td>A.D.</td>
<td>7.4</td>
<td>4.0</td>
<td>3.4</td>
<td>70</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>9</td>
<td>G.W.</td>
<td>10.0</td>
<td>4.0</td>
<td>6.0</td>
<td>30</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>10</td>
<td>J.R.</td>
<td>11.0</td>
<td>4.8</td>
<td>6.2</td>
<td>35</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>11</td>
<td>J.M.</td>
<td>6.4</td>
<td>5.0</td>
<td>3.4</td>
<td>45</td>
<td>- 2</td>
<td>---</td>
</tr>
<tr>
<td>12</td>
<td>J.E.</td>
<td>8.7</td>
<td>5.2</td>
<td>3.5</td>
<td>56</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>13</td>
<td>R.E.</td>
<td>9.0</td>
<td>4.2</td>
<td>4.8</td>
<td>80</td>
<td>- 2</td>
<td>---</td>
</tr>
<tr>
<td>14</td>
<td>M.R.</td>
<td>10.2</td>
<td>4.6</td>
<td>5.6</td>
<td>45</td>
<td>- 1</td>
<td>---</td>
</tr>
<tr>
<td>15</td>
<td>D.M.</td>
<td>9.6</td>
<td>6.6</td>
<td>2.8</td>
<td>45</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>16</td>
<td>E.C.</td>
<td>9.6</td>
<td>7.0</td>
<td>2.8</td>
<td>124</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>17</td>
<td>P.A.</td>
<td>12.0</td>
<td>4.0</td>
<td>8.0</td>
<td>50</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>18</td>
<td>J.F.</td>
<td>9.9</td>
<td>5.4</td>
<td>4.5</td>
<td>125</td>
<td>+ 1</td>
<td>---</td>
</tr>
<tr>
<td>19</td>
<td>J.G.</td>
<td>11.4</td>
<td>5.5</td>
<td>5.9</td>
<td>54</td>
<td>+ 2</td>
<td>---</td>
</tr>
<tr>
<td>20</td>
<td>J.M.</td>
<td>14.0</td>
<td>5.9</td>
<td>8.1</td>
<td>22</td>
<td>- 3</td>
<td>---</td>
</tr>
<tr>
<td>21</td>
<td>T.D.</td>
<td>11.1</td>
<td>5.3</td>
<td>5.8</td>
<td>46</td>
<td>- 2</td>
<td>---</td>
</tr>
<tr>
<td>22</td>
<td>H.A.</td>
<td>11.1</td>
<td>5.7</td>
<td>5.4</td>
<td>53</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>23</td>
<td>J.A.</td>
<td>9.4</td>
<td>5.2</td>
<td>4.3</td>
<td>50</td>
<td>+ 1</td>
<td>---</td>
</tr>
<tr>
<td>24</td>
<td>W.B.</td>
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<td>5.2</td>
<td>5.8</td>
<td>85</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>25</td>
<td>C.N.</td>
<td>9.8</td>
<td>4.9</td>
<td>5.8</td>
<td>50</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>26</td>
<td>M.C.</td>
<td>10.5</td>
<td>4.2</td>
<td>6.3</td>
<td>50</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>27</td>
<td>J.T.</td>
<td>10.3</td>
<td>5.2</td>
<td>5.1</td>
<td>50</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>28</td>
<td>F.L.</td>
<td>12.4</td>
<td>4.8</td>
<td>7.6</td>
<td>50</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>29</td>
<td>G.S.</td>
<td>12.2</td>
<td>4.8</td>
<td>6.5</td>
<td>46</td>
<td>- 2</td>
<td>---</td>
</tr>
<tr>
<td>30</td>
<td>A.M.</td>
<td>13.1</td>
<td>7.4</td>
<td>5.9</td>
<td>72</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>31</td>
<td>F.R.</td>
<td>8.4</td>
<td>4.4</td>
<td>4.0</td>
<td>32</td>
<td>- 3</td>
<td>---</td>
</tr>
<tr>
<td>32</td>
<td>J.E.</td>
<td>9.6</td>
<td>6.6</td>
<td>3.0</td>
<td>60</td>
<td>- 2</td>
<td>---</td>
</tr>
<tr>
<td>33</td>
<td>J.R.</td>
<td>10.0</td>
<td>5.8</td>
<td>4.2</td>
<td>75</td>
<td>0</td>
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</tr>
<tr>
<td>34</td>
<td>A.M.</td>
<td>11.0</td>
<td>5.0</td>
<td>5.2</td>
<td>80</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>35</td>
<td>G.W.</td>
<td>7.6</td>
<td>6.0</td>
<td>2.6</td>
<td>52</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>36</td>
<td>F.G.</td>
<td>8.3</td>
<td>3.9</td>
<td>4.4</td>
<td>55</td>
<td>- 3</td>
<td>---</td>
</tr>
<tr>
<td>37</td>
<td>C.D.</td>
<td>10.8</td>
<td>4.2</td>
<td>6.6</td>
<td>32</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>38</td>
<td>N.F.</td>
<td>11.1</td>
<td>4.8</td>
<td>6.3</td>
<td>54</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>39</td>
<td>D.F.</td>
<td>9.0</td>
<td>4.0</td>
<td>5.0</td>
<td>64</td>
<td>- 2</td>
<td>---</td>
</tr>
<tr>
<td>40</td>
<td>O.A.</td>
<td>13.2</td>
<td>4.6</td>
<td>8.8</td>
<td>70</td>
<td>0</td>
<td>---</td>
</tr>
</tbody>
</table>

Mean 10.43 5.12 5.30 57.37
Range 7.3 - 14.0 3.7 - 7.5 2.6 - 8.6 22 - 125
Standard deviation 1.47 0.99 1.43 24.67
Standard error of mean 0.208 0.140 0.202 3.524
Coefficient of variation 14.09 10.54 26.98 43.00

* Interval between serial records varies from 6 days to 4 weeks.
+ = Oedema apparent by pitting on pressure.
++ = Obvious oedema, more extensive than above.
--- = No apparent oedema.
and beyond was excluded. As age advances emphysema (as it is encountered in the wards and outpatient departments of a large general hospital) is increasingly accompanied by degenerative changes elsewhere, notably in the systemic and coronary arterial systems. (This is irrespective of whatever structural change there may be in the pulmonary vessels which, for this consideration, is regarded as part of the primary pathology of emphysema). Extra-pulmonary vascular degeneration of the kind referred to is common, moreover, at an age when the natural degenerative changes of senescence are not usually expected so that one is led, perhaps too simply, to wonder if a common cause does not underlie pulmonary emphysema and (a variety of) athero-sclerosis, or whether the latter may not be a consequence of the former. The opposite suggestion that emphysema is secondary to poor nutrition caused by vascular changes in the pulmonary (and systemic) circulation has been deprecated by Christie (1944).

Of the 40 patients with emphysema comprising this group the youngest was aged 16, the eldest 75, and twenty-seven were over the age of 40. The inclusion of one so young should be considered in the light of what has already been said of semi-permanent pulmonary distension as distinct from the anatomical change that constitutes true emphysema. It is known that the former occurs in young asthmatics associated with an inspiratory position of the chest and that this can
### TABLE VIII

**DIFFERENCE BETWEEN CORRESPONDING MEANS IN EMPHYSEMA AND CONTROLS**

<table>
<thead>
<tr>
<th></th>
<th>MEAN IN CONTROLS (a)</th>
<th>MEAN IN EMPHYSEMA (b)</th>
<th>ARITHMETICAL DIFFERENCE BETWEEN a and b</th>
<th>STANDARD ERROR OF DIFFERENCE</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm to tongue time (seconds)</td>
<td>12.02</td>
<td>10.43</td>
<td>1.59</td>
<td>0.305</td>
<td>5.213</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Arm to lung time (seconds)</td>
<td>4.73</td>
<td>5.12</td>
<td>0.39</td>
<td>0.219</td>
<td>1.781</td>
<td>.1, .05</td>
</tr>
<tr>
<td>Lung to tongue time (seconds)</td>
<td>7.28</td>
<td>5.30</td>
<td>1.98</td>
<td>0.316</td>
<td>6.266</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Brachial venous pressure (mm. blood above sternal angle)</td>
<td>17.40</td>
<td>57.37</td>
<td>39.97</td>
<td>3.715</td>
<td>10.751</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
long predate irreversible vesicular emphysema. What is in question is whether such functional distension of the lungs can produce the spirometric pattern of emphysema which thus becomes reversible. Twelve had a systolic blood pressure of 150 mm. Hg. or more and/or a diastolic pressure of 90 mm. Hg. or more; 17 had significant electrocardiographic changes (in one or more of leads I, II, III, C5F, IV,F), and 10 had demonstrable enlargement of the heart in routine teleradiograms. In only four of the latter was the enlargement considered exclusively to affect the right ventricle, pulmonary conus or artery.

Eight of the 40 had peripheral oedema of varying extent. The occurrence of oedema or its degree did not apparently correlate with the estimated venous pressure or the duration of any circulation time.

Comparison of results in emphysema and in controls. Comparison of the observations in emphysema (Table VII) with those in the controls (Table VI) is facilitated by reference to Table VIII (opp. p. 84).

The conventional level of significance is a value of $P = 0.05$ or, what is approximately the same, a difference between means which is twice the standard error of the difference. Such a difference would, in fact, be expected to occur by chance once in 20 times; a difference $2\frac{1}{2}$ times its standard error would arise by chance once in 80 occasions and if three times the standard error only once in 370. Correspondingly, as
the value of $P$ diminishes so does the probability of chance occurrence. When $P = .01$ this probability is once in 100; when equal to .001 once in 1000.

It is apparent that in emphysema compared to the controls (1) arm to tongue time is less, (2) lung to tongue time is less, and (3) brachial venous pressure is greater. There is no significant difference in arm to lung time. In no individual of either group did manual compression of the abdomen cause brachial venous pressure to alter appreciably. Within the trivial range observed (+ 3 to −3 mm. of water) the direction of change was erratic in both groups.

**Emphysema with congestive heart failure.** Records of circulation times and venous pressure in emphysema with congestive heart failure are listed and analysed in Table IX, and these in turn are compared with the corresponding observations in the other two groups in Table X (opp. p. 89).

As a preliminary to the consideration of these figures further comment on the selection of material for this group is necessary. The original intention was to limit it to patients with congestive heart failure caused, so far as could be made out, by emphysema and without other lesion that might have any significance in the genesis of heart failure. It became apparent in time that selection of patients
## TABLE IX

CIRCULATION TIMES AND BRACHIAL VENOUS PRESSURE IN EMPHYSEMA WITH CONGESTIVE HEART FAILURE

<table>
<thead>
<tr>
<th>CASE NUMBER</th>
<th>PATIENT</th>
<th>ARM TO TONGUE TIME IN SECONDS</th>
<th>ARM TO LUNG TIME IN SECONDS</th>
<th>LUNG TO TONGUE TIME IN SECONDS</th>
<th>BRACHIAL VENOUS PRESSURE (V.P.) IN MM. BLOOD ABOVE STERNAL ANGLE</th>
<th>CHANGE IN BRACHIAL V.P. IN MM. BLOOD CAUSED BY COMPRESSION OF ABDOMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>R.E.</td>
<td>16.4</td>
<td>9.3</td>
<td>7.1</td>
<td>90</td>
<td>+ 70</td>
</tr>
<tr>
<td>52</td>
<td>J.N.</td>
<td>18.8</td>
<td>13.1</td>
<td>5.7</td>
<td>250</td>
<td>&gt; + 50*</td>
</tr>
<tr>
<td>53</td>
<td>A.B.</td>
<td>15.5</td>
<td>9.7</td>
<td>5.8</td>
<td>160</td>
<td>+ 90</td>
</tr>
<tr>
<td>54</td>
<td>E.McK(1)</td>
<td>-</td>
<td>-</td>
<td>5.8</td>
<td>300</td>
<td>+ 150</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>J.K.</td>
<td>22.5</td>
<td>16.4</td>
<td>6.1</td>
<td>210</td>
<td>+ 145</td>
</tr>
<tr>
<td>56</td>
<td>T.M. (1)</td>
<td>18.1</td>
<td>5.0</td>
<td>9.5</td>
<td>85</td>
<td>+ 30</td>
</tr>
<tr>
<td></td>
<td>(2)</td>
<td>13.5</td>
<td>4.0</td>
<td>9.5</td>
<td>85</td>
<td>+ 15</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>G.P.</td>
<td>19.5</td>
<td>14.0</td>
<td>5.5</td>
<td>150</td>
<td>+ 40</td>
</tr>
<tr>
<td>58</td>
<td>P.E. (1)</td>
<td>21.4</td>
<td>16.2</td>
<td>5.2</td>
<td>80</td>
<td>+ 81</td>
</tr>
<tr>
<td></td>
<td>(2)</td>
<td>23.0</td>
<td>19.0</td>
<td>5.0</td>
<td>164</td>
<td>+ 48</td>
</tr>
<tr>
<td></td>
<td>(3)</td>
<td>25.4</td>
<td>17.0</td>
<td>8.4</td>
<td>15</td>
<td>+ 35</td>
</tr>
<tr>
<td></td>
<td>(4)</td>
<td>24.6</td>
<td>16.8</td>
<td>7.8</td>
<td>25</td>
<td>+ 27</td>
</tr>
<tr>
<td></td>
<td>(5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>59</td>
<td>D.M. (1)</td>
<td>20.1</td>
<td>15.0</td>
<td>5.1</td>
<td>110</td>
<td>+ 155</td>
</tr>
<tr>
<td></td>
<td>(2)</td>
<td>16.0</td>
<td>11.1</td>
<td>4.9</td>
<td>27</td>
<td>+ 67</td>
</tr>
<tr>
<td></td>
<td>(3)</td>
<td>17.4</td>
<td>11.3</td>
<td>6.1</td>
<td>Not recorded</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(4)</td>
<td>11.6</td>
<td>6.8</td>
<td>4.8</td>
<td>Not recorded</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(5)</td>
<td>11.9</td>
<td>5.8</td>
<td>6.1</td>
<td>Not recorded</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>J.C. (1)</td>
<td>26.6</td>
<td>20.3</td>
<td>6.3</td>
<td>170</td>
<td>+ 70</td>
</tr>
<tr>
<td></td>
<td>(2)</td>
<td>16.2</td>
<td>10.8</td>
<td>5.4</td>
<td>125</td>
<td>+ 75</td>
</tr>
<tr>
<td></td>
<td>(3)</td>
<td>35.2</td>
<td>18.7</td>
<td>16.5</td>
<td>Not recorded</td>
<td></td>
</tr>
<tr>
<td></td>
<td>X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>D.P. (1)</td>
<td>19.6</td>
<td>13.1</td>
<td>6.5</td>
<td>180</td>
<td>+ 70</td>
</tr>
<tr>
<td></td>
<td>(2)</td>
<td>17.8</td>
<td>11.2</td>
<td>6.6</td>
<td>125</td>
<td>+ 75</td>
</tr>
<tr>
<td></td>
<td>(3)</td>
<td>11.6</td>
<td>6.8</td>
<td>4.8</td>
<td>25</td>
<td>+ 20</td>
</tr>
<tr>
<td>62</td>
<td>J.M. (1)</td>
<td>16.4</td>
<td>10.9</td>
<td>5.5</td>
<td>55</td>
<td>+ 75</td>
</tr>
<tr>
<td></td>
<td>(2)</td>
<td>27.0</td>
<td>16.0</td>
<td>11.0</td>
<td>230</td>
<td>&gt; + 70 *</td>
</tr>
</tbody>
</table>

| Mean        | 19.42    | 12.43                        | 6.83                       | 123.13                          | + 76.66                        |
| Range       | 5.62     | 4.65                         | 2.79                       | 15-300                           | + 10 to + 160                  |
| Standard deviation | 5.62  | 4.65                         | 2.79                       | 89.18                            | 45.98                          |
| Standard error of mean | 1.15 | 0.95                         | 0.54                       | 18.20                            | 9.40                          |
| Co-efficient of variation | 28.93 | 37.42                        | 40.82                       | 72.42                            | .59.98                       |
Manometer used on these occasions was graduated to 300 mm. only. A considerable increase of pressure beyond this limit was apparent but not measurable.

Decholin and ether times were measured from dorsum of hand because antecubital veins were obscured. Hence arm to tongue and arm to lung times are not comparable with others in table but lung to tongue time is.

This record was taken only 2 hours before death. Patient had until then progressed favourably but on this day developed acute precordial pain and left ventricular failure.
on this principle excluded most cases usually diagnosed as cor pulmonale and that the pure syndrome of emphysema heart failure was strikingly rare - an observation that is by no means novel (White and Brenner, 1933). It accords with the experience of Parkinson and Hoyle (1937) in whose series of 80 patients with high grade emphysema, observed over a period of 2-3 years, only 13 developed congestive heart failure. This group therefore has come to be made up from patients diagnosed clinically as cor pulmonale in whom the presence of emphysema was confirmed, in whom emphysema appeared to be the direct cause of heart failure, and in whom co-existing hypertension or atherosclerosis was considered unlikely to have caused heart failure had it existed alone. On this basis of selection 12 patients were available for investigation over a period of approximately 2 years. Although these patients were assiduously sought it is not intended, for various reasons, that this figure should be interpreted as portraying the incidence of this form of heart failure. Of the twelve only 4 could reasonably be described as the pure syndrome, i.e. in that they had no other discoverable cardio-vascular lesion, albeit how minor, that might critically be considered to have contributed to the development of heart failure.

When admitted to hospital all patients with emphysema heart failure had cyanosis and oedema of
Figures 3 and 4 Overleaf
Figure 3

Spirometric tracing from a patient (Case 59) with typical right heart failure of emphysema. The characteristic spirometric pattern of emphysema is preserved (cf. Figs. 1 and 2).

Figure 4

Record from same patient (Case 59) taken 9 days later at a time when he was very much better clinically and conspicuous signs of heart failure had disappeared. The striking absence of appreciable change in respiratory efficiency implies that the pulmonary circulation and left heart are spared in this variety of heart failure. Unprolonged lung to tongue time has the same significance on purely circulatory standards.
varying degree. All were dyspneic at rest but only one was orthopneic (Case 56). He was a previously known patient whose disability had appeared to be determined by emphysema although he also was hypertensive. Two more became orthopneic subsequently with the development of acute left ventricular failure from which they died. These will be referred to again presently.

In the presence of congestive heart failure emphysema preserves its characteristic spirometric pattern (Fig. 3). It has been suggested (Christie 1934) that cardiac failure associated with chronic pulmonary venous congestion may itself cause emphysema by reason of diminished distensibility of the lungs, overstretching of surface alveoli and consequent loss of elasticity. Be this as it may, there is every indication in all the patients included in this group that the emphysema preceded congestive failure by a long period of time.

Seven of the twelve patients died during the single period of hospitalisation; four of them, including three graded as pure cor pulmonale (Cases 52, 53, and 55, Table IX) died within 48 hours of their admission. The fourth apparently uncomplicated heart failure of emphysema (Case 59) has been under observation for more than a year.

One patient (Case 60) after improving for a time, developed acute left ventricular failure following a coronary thrombosis and died two hours later. The right heart failure/
of another developed into a progressive failure of the whole heart associated with an insidiously advancing lobar pneumonia. Records of circulation time in the phase of superadded left ventricular failure are included in the statistical calculations (Tables IX and X). Both these instances will tend to vitiate the characteristic features of cor pulmonale as will be shown. The other five died from progression of their initial heart failure which preserved its pattern to the end (Cases 51, 52, 53, 54 and 55).

Table IX is an analysis of all the observations made in this group and therefore includes records from patients apparently recovered from the acute episode (heart failure) that necessitated their admission to hospital as well as from others who were at the time moribund. There are 24 such observations on arm to tongue and arm to lung times and 27 on lung to tongue time. The reason for the difference is that one patient had the decholin and other injected into a vein on the volar surface of the wrist because, owing to oedema (and obesity), the antecubital veins were inaccessible. The wrist to tongue and wrist to lung times thus registered are not comparable with any other; the lung to tongue time, the difference between these two, is unaffected by the site of injection. Venous pressure recordings are also limited to 24 on account of technical difficulties.
### TABLE X

DIFFERENCE BETWEEN CORRESPONDING MEANS IN:

(a) Controls and Emphysema with Congestive Heart Failure.

<table>
<thead>
<tr>
<th></th>
<th>MEAN IN CONTROLS (a)</th>
<th>MEAN IN EMPHYSEMA WITH HEART FAILURE (b)</th>
<th>ARITHMETICAL DIFFERENCE BETWEEN a and b</th>
<th>STANDARD ERROR OF DIFFERENCE</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm to tongue time (seconds)</td>
<td>12.02</td>
<td>19.42</td>
<td>7.40</td>
<td>1.168</td>
<td>6.336</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Arm to lung time (seconds)</td>
<td>4.73</td>
<td>12.43</td>
<td>7.70</td>
<td>0.964</td>
<td>7.988</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lung to tongue time (seconds)</td>
<td>7.28</td>
<td>6.83</td>
<td>0.45</td>
<td>0.589</td>
<td>0.764</td>
<td>&lt;.5, &gt;.4</td>
</tr>
<tr>
<td>Brachial venous pressure (mm. blood above sternal angle)</td>
<td>17.40</td>
<td>123.13</td>
<td>105.73</td>
<td>18.248</td>
<td>5.794</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

(b) Uncomplicated Emphysema and Emphysema with Congestive Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>MEAN IN EMPHYSEMA (a)</th>
<th>MEAN IN EMPHYSEMA WITH HEART FAILURE (b)</th>
<th>ARITHMETICAL DIFFERENCE BETWEEN a and b</th>
<th>STANDARD ERROR OF DIFFERENCE</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm to tongue time (seconds)</td>
<td>10.43</td>
<td>19.42</td>
<td>8.99</td>
<td>1.165</td>
<td>7.717</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Arm to lung time (seconds)</td>
<td>5.12</td>
<td>12.43</td>
<td>7.31</td>
<td>0.960</td>
<td>7.615</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lung to tongue time (seconds)</td>
<td>5.30</td>
<td>6.83</td>
<td>1.53</td>
<td>0.574</td>
<td>2.666</td>
<td>&lt;.01, &gt;.001</td>
</tr>
<tr>
<td>Brachial venous pressure (mm. blood above sternal angle)</td>
<td>57.37</td>
<td>123.13</td>
<td>65.76</td>
<td>18.534</td>
<td>3.548</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Comparison of results in the three groups. It is obvious (Table X) that in the group of emphysema with congestive heart failure arm to tongue and arm to lung times are, as would be expected, greater than in uncomplicated emphysema and greater than in health. Brachial venous pressure is likewise higher than in these. The mean lung to tongue time is, in this small group of emphysema with heart failure, less than the corresponding time in the normal, though not significantly so. What is greatly significant is that the lung to tongue time is not prolonged, that is that the pulmonary circulation is not retarded.

Relative to uncomplicated emphysema, however, lung to tongue time is significantly prolonged. In every individual classified as emphysema heart failure abdominal compression caused an increase in brachial venous pressure (Table IX). In all, when they came under observation, this increase was so pronounced as never to be equivocal.

Figure 5 represents graphically the frequency distribution of lung to tongue time in each of the 3 groups. The striking thing about the distribution is that uncomplicated emphysema and emphysema with congestive heart failure have a common mode, which is less than that of the controls. Furthermore there are three values of the variate (11.0, 13.1 and 16.5 seconds) which lie outside the otherwise symmetrical
Figure 5

Frequency Distribution of Lung to Tongue Time in Controls, Uncomplicated Emphysema and Emphysema Heart Failure.

It is noteworthy that:

(1) both groups of emphysema have a common mode (which is less than that of the controls);

(2) the 3 observations outwith the symmetrical distribution are from 3 patients in whom left ventricular failure from other causes was known to have become superimposed terminally in two of these.
**TABLE XI**

**RE-ASSESSMENT OF SIGNIFICANCE OF DIFFERENCE BETWEEN MEAN LUNG TO TONGUE TIMES IN THE 3 GROUPS AFTER OMission OF THE 3 OUTLYING OBSERVATIONS IN HISTOGRAM (FIG: 5)**

<table>
<thead>
<tr>
<th></th>
<th>LUNG TO TONGUE TIME (ONLY)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN IN</td>
<td>MEAN IN</td>
<td>MEAN IN</td>
<td>ARITHMETICAL</td>
<td>STANDARD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CONTROLS,</td>
<td>EMPHYSEMA,</td>
<td>EMPHYSEMA</td>
<td>DIFFERENCE</td>
<td>ERROR OF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SECONDS.</td>
<td>SECONDS.</td>
<td>HEART</td>
<td>BETWEEN</td>
<td>DIFFERENCE.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FAILURE</td>
<td>MEANS.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SECONDS.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Controls</td>
<td>7.28</td>
<td>---</td>
<td>5.92</td>
<td>1.36</td>
<td>0.345</td>
<td>3.652</td>
</tr>
<tr>
<td>and emphysema</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>heart failure.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Uncomplicated</td>
<td>---</td>
<td>5.30</td>
<td>5.92</td>
<td>0.62</td>
<td>0.318</td>
<td>1.949</td>
</tr>
<tr>
<td>emphysema and</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>emphysema heart</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>failure.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After exclusion of the 3 observations referred to the mean lung to tongue time in heart failure of emphysema ceases to be significantly longer than that in uncomplicated emphysema, and at the same time becomes significantly less than that of the controls.
distribution curves. Two of these "aberrant" values derive from the patients already referred to as having clinically diagnosable superadded failure of the left heart at the time when these particular observations were made; the third is from the only patient who was orthopnoeic when admitted and was previously known to be hypertensive. Table XI shows a further comparison of mean lung to tongue times in the various groups and a re-assessment of the significance of differences between them after the three observations in question have been omitted. The implications are (1) that there is no significant change in the lung to tongue time of emphysema with the development of heart failure directly due to that emphysema and (2) that the difference between the lung to tongue time of emphysema with heart failure and that of the controls becomes significant, that is that in the presence of emphysema, even after it has caused heart failure, the pulmonary circulation is actually faster than it is in health.

Comparison of results in heart failure of emphysema with corresponding records in rheumatic heart failure. The relevant figures for this comparison appear in Tables XII and XIII.

Arm to tongue time in rheumatic heart failure is twice as long as it is in the heart failure of emphysema notwithstanding that peripheral venous pressure
TABLE XII

SEGMENTAL CIRCULATION TIMES AND BRACHIAL VENOUS PRESSURE IN RHEUMATIC HEART FAILURE

<table>
<thead>
<tr>
<th></th>
<th>Arm to tongue time, seconds</th>
<th>Arm to lung time, seconds</th>
<th>Lung to tongue time, seconds</th>
<th>Brachial venous pressure, mm. blood above sternal angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>39.27</td>
<td>20.19</td>
<td>19.10</td>
<td>99.03</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>22.63</td>
<td>13.38</td>
<td>14.08</td>
<td>52.33</td>
</tr>
</tbody>
</table>
is equally raised in both. In rheumatic heart failure also the increase in circulation time is gross over both arm to lung and lung to tongue segments; the greater prolongation will occur over one or other segment in proportion as the failure is dominantly of the right or left side of the heart (Fishberg et al., 1933; Plotz, 1939). In emphysema heart failure, on the other hand, only arm to lung time is prolonged beyond normal values (Table X) and, even so, this is scarcely more than half the corresponding time in rheumatic heart failure. Relative to uncomplicated emphysema however the lung to tongue time in emphysema heart failure may be prolonged, though still within normal limits (Table X). From this and previous comment on lung to tongue times (page 88-89) the indications are that the nearer the syndrome of heart failure approaches that of pure cor pulmonale not only is the pulmonary circulation not retarded relative to the normal but it may, as in uncomplicated emphysema, be accelerated.

What has just been written of rheumatic heart failure has been proved equally true of hypertensive heart failure (the two being, dynamically, similar). It would be redundant to record the figures in detail.

It is perhaps possible (though not encountered in this investigation) that in an individual case of left ventricular failure from hypertensive or rheumatic
heart disease arm to tongue time may be equally brief as in some cases of emphysema with heart failure, but it is most unlikely that lung to tongue time will ever be so.
# TABLE XIII

**DIFFERENCE BETWEEN CORRESPONDING MEANS IN**

**EMPHYSEMA HEART FAILURE AND IN RHEUMATIC HEART FAILURE**

<table>
<thead>
<tr>
<th>Time Type</th>
<th>Mean in Emphysema Heart Failure (a)</th>
<th>Mean in Rheumatic Heart Failure (b)</th>
<th>Arithmetical Difference between a and b</th>
<th>Standard Error of Difference</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm to tongue time (seconds)</td>
<td>19.42</td>
<td>39.27</td>
<td>19.85</td>
<td>4.224</td>
<td>4.699</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Arm to lung time (seconds)</td>
<td>12.43</td>
<td>20.39</td>
<td>7.76</td>
<td>2.583</td>
<td>3.004</td>
<td>&lt;.01, &gt;.001</td>
</tr>
<tr>
<td>Lung to tongue time (seconds)</td>
<td>6.83</td>
<td>19.1</td>
<td>12.27</td>
<td>2.585</td>
<td>4.747</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Brachial venous pressure (mm. blood above sternal angle)</td>
<td>123.13</td>
<td>99.03</td>
<td>24.10</td>
<td>20.487</td>
<td>1.128</td>
<td>&lt;.3, &gt;.2</td>
</tr>
</tbody>
</table>
DISCUSSION

To invoke simple physical laws in the interpretation of complex biological phenomena may seem to imply too naive a conception of the mammalian organism. The dynamics of a rigid hydraulic system conform accurately to Poisseeuille's equation; those of naturally circulating blood, contained in a system of branching, distensible tubes, do not wholly. In contrast to the rigidity of the physical system vascular diameters decrease progressively to a minimum and then increase again; they also are in large part reflexly variable. The justification for applying a law of this kind to the vascular system of man is the absence of any better and the acknowledgement by the observer of its limitations, and still more of his own.

Elementarily the motion of blood within the vascular channels is comparable to that of liquid within a closed system of cylindrical tubes. As such the linear velocity of blood flow in any part of the circulation is inversely proportional to the cross-sectional area of the part concerned, and the velocity of blood flow as a whole varies directly with the volume flow. The latter in turn is determined directly by the pressure head and inversely by the resistance of the tube system. The constancy of several factors must be assumed and that justifiably, not so much because they are strictly constant as because their
variability is unpredictable and, at present, immeasurable.

Although the diameter of blood vessels decreases from the heart to the periphery the total cross sectional area increases at the same time, and in the capillary bed increases enormously. Individual capillaries have a diameter scarcely more than that of a red blood corpuscle and an average length of 0.5 mm. yet the total cross sectional area of the systemic capillaries has been variously estimated as 300 to 800 times that of the aorta (Wiggers, 1940). The velocity of blood flow is decreased proportionately. That this is so has been confirmed by micro-observation of living tissues. In the lungs the capillaries form a continuous network of maximum area which has been calculated as 140 square metres in man, but there are "no capillary units of independent length" as such (Drinker, 1946). Appreciation of this fact is important for the word "capillaries" applied to the circulation naturally suggests long, tenuous, individual channels which do not, in fact, exist in any tissue. In the pulmonary circulation, therefore, which is normally the only available channel for blood flowing from the right side of the heart to the left (and as much passes this way in unit time as through the systemic circulation, except for temporary variations) a reduction in the cross-sectional area of the vascular bed, so long as there is no accompanying fall
in cardiac output, will tend to cause the velocity of blood flow through the lungs to be increased; and that without necessarily any change in the volume of pulmonary blood flow. That the capillary area is reduced in the emphysematous lung was known to Virchow (1858), was described in detail by Isaakssohn (1871) and re-described, without much variation, by numerous writers who succeeded him. Theoretically, therefore, the basis for a faster pulmonary circulation exists in emphysema. The present investigation has established that a faster circulation exists.

On the other hand it is characteristic of the systemic circulation that an increased resistance in one part is compensated by vasodilatation in another. There is little doubt but that there are vasomotor nerves in the lungs (Daly and Ruler, 1932), but the evidence for their exercising any significant control over blood flow is less convincing. Nor is such control considered necessary (Hamilton, Woodbury and Vogt, 1939; Hamilton, 1940). The pulmonary blood vessels are so distensible that the lungs can accommodate any increase in blood content by passive increase in diameter of individual vessels already open and by opening up of new ones (Drinker, Churchill and Ferry, 1926). Assuming that under conditions of maximal physiological demands the vascular system of the lungs is filled to the limit of its capacity, then only under the same exacting conditions would a
greater pulmonary resistance become operative in minimal emphysema. Theoretically, as the disease progressed so would the increased resistance become effective at a lower level of effort until eventually it was so at rest. But the pulmonary capillary network and alveolar surface are so vast (the latter is considered to amount to 90 square metres, comprising 750 million alveolar units, in an adult man (Drinker, 1946)) that the employment of the whole is never necessary under physiological conditions. There is an absolute pulmonary reserve and so long as this exists there is no necessity for a faster circulation. Patients with minimal emphysema do not occupy hospital beds nor, in fact, do those with significant breathing reserve beyond their resting requirements. In that advanced stage of emphysema the diminished vascular area of the lungs would contribute to a faster pulmonary circulation.

Spontaneous variations in the circulation are both purposive and beneficial. Local acceleration of blood flow through the pulmonary capillaries would of itself serve no useful purpose if the volume flow remained unchanged. Any influence of the increased resistance would be to reduce the latter and the resultant velocity would be a compromise. The need in emphysema is to preserve or to restore the oxygen saturation of arterial blood. This can only
be assured by an increase both in volume and velocity of blood flow through the lungs. The diminished arm to tongue (and lung to tongue) time implies that both are increased (Blumgart, 1931; Fishberg et al., 1933). It has been calculated (Roughton, 1945) that the time taken in each circulatory cycle to establish perfect gaseous equilibrium between capillary blood and alveolar air is approximately 0.75 second at rest and 0.34 second during strenuous exercise. The time requirement for gaseous exchange does not therefore set a limit to a faster pulmonary blood flow within a wide range of acceleration and certainly not within the range of circulation times recorded in this investigation.

Arm to lung time includes the unknown time of diffusion of ether. For this reason alone it would be expected to be less accurate than decholin time. Their respective co-efficients of variation (24.3 and 12.9) bear this out. Any contribution of emphysema to increase this error would be by way of prolonging the diffusion time and therefore the recorded arm to lung time. That the latter is not significantly prolonged is the more striking in consequence.

It has been shown (Table VII) that in emphysema peripheral venous pressure is increased considerably. This has previously been recorded (Kountz et al. 1929, 1932, 1934; Christie, 1934) as has distension of neck veins (Parkinson and Hoyle, 1937), although most
writers on emphysema have described venous pressure as being unaltered or even reduced (Master, Jaffe and Dack, 1935; Durant, 1946), or have made no mention of it. Blumgart and Weiss (1927) who made the significant observation that pulmonary blood flow is not retarded in the presence of emphysema believed that peripheral venous pressure is unaffected by this disease. Inevitably their further study of emphysema presented them with anomalous combinations of high venous pressure and short circulation time which apparently conflicted with the principle that they had already established viz. that congestive heart failure implies that venous pressure is raised and circulation time prolonged. They felt constrained accordingly to modify this dictum to the extent that when occurring with emphysema either a raised venous pressure or a prolonged circulation time is diagnostic of heart failure "even in the absence of oedema or other clinical evidence of congestive failure." Nor was this in accord with their valid argument that in the evolution of congestive heart failure circulation time is prolonged before venous pressure rises (Blumgart, 1931).

Because the velocity of blood flow is inversely proportional to the cross-sectional area of the vascular bed it therefore decreases from the heart to the capillaries, speeding up again as the blood
enters the less capacious venules. In contrast the lateral pressure throughout the vascular system is, on the same physical basis, determined by the resistance to flow offered by individual vessels and therefore continues to diminish progressively beyond the capillaries until the heart is reached. Accordingly, the pressure recorded at any point of the venous system represents the remnant of the pressure imparted by ventricular systole (persisting to that particular point) plus the pressure existing in the right auricle at that time.

The venous inflow to the heart is dependent on the existence of a pressure in the veins greater than that in the auricles (Henderson, 1906). So long as venous pressure is an index of inflow the output of the healthy heart is governed directly by venous pressure (Starling, 1918). More comprehensively, cardiac output, "within the limits of compensation", is determined by central or intra-aortic venous pressure (Wiggers, 1940). The truth of this has been verified in man by auricular catheterisation (McMichael and Sharpay-Schafer, 1944; Barcroft, Edholm, McMichael and Sharpay-Schafer, 1944).

Auricular and peripheral venous pressures vary with changes in intra-pleural (intra-thoracic) pressure, which is normally sub-atmospheric, but not proportionately (Wiggers, 1940). There is a small but perceptible rise and fall of peripheral venous
pressure in quiet expiration and inspiration respectively. This phasic variation is more pronounced during deep breathing. During rapid breathing, whether shallow or deep, venous pressure is reduced (Lyons, Burwell, and Kennedy, 1938) as it is in the laboured breathing of tracheal obstruction (Richards, Courmand, Darling Gillespie, and Baldwin, 1942). Apnoea is accompanied by an increase in venous pressure (Lyons et al., 1938). It rises considerably in the Valsalva experiment (Myer and Middleton, 1929, Kountz, Pearson and Koenig, 1932; Winsor and Burch, 1946) and it is usually said to fall correspondingly during the Müller experiment. There is however a striking lack of detailed information in reports of the Müller effect in comparison with the other. It was noted during the present investigation that venous pressure fell to a small extent during obstructed inspiration but rose again to the original level or a higher if the effort could be maintained, whereas in obstructed expiration an increase was invariable and pressures of 300-400 mm. of water were frequently obtained. A negative pressure was not producible under any circumstances including vertical elevation of the arm. This accords with the previous observations of Doupe, Krynauw and Snodgrass (1938), and conflicts with those of Lewis (1930, 1944) and Clark, Hooker and Weed (1934). Nor indeed is a negative (sub-atmospheric) pressure
possible in extra-thoracic veins for they must inevitable collapse at atmospheric pressure and blood flow ceases. If this occurs the circumstances producing it must imply a degradation of pressure energy to zero and the hydrostatic pressure in the auricle and intra-thoracic veins must be nil.

It is apparent that a significant venous pressure gradient from the periphery to the heart must exist under physiological conditions. The average gradient from basilic vein to right auricle in man has been estimated as 41 mm. of water (Richards et al. 1942). Winsor and Burch (1946) provide average figures for pressure in various veins from which it is calculable that the gradient from the dorsal metacarpal to the median basilic vein is 23 mm., and from the dorsalis pedis to the femoral vein 65 mm., of water. Positive pressure breathing is associated with a reduction in venous gradient, auricular pressure being increased by a greater amount than is the pressure in the peripheral veins, both in animals and in man (Holt, 1943, 1944; Richards, 1945; Car and Essex, 1946). During negative pressure breathing auricular pressure falls considerably and the peripheral pressure less so, so that the venous gradient is increased. In right ventricular failure the venous gradient is decreased and auricular pressure may equal or exceed peripheral venous pressure (Richards et al., 1942).
Otis, Rahn and Fenn (1946) showed that peripheral venous pressure during positive pressure breathing increases in a predictable manner. Equally does it fall predictably with negative pressure breathing to the limit set by the hydrostatic pressure in the intra-thoracic (central) veins above the zero reference plane adopted. Nor can absolute auricular pressure, irrespective of what the effective venous pressure may be, fall below this (positive) hydrostatic equivalent. Thus intra-thoracic pressure is a potent influence in altering both auricular and peripheral venous pressures. These vary in the same direction but not in parallel, and neither is, strictly, a true index of venous filling under all conditions "up to the point of decompensation".

When pressures in the circulation are measured by manometer balanced against atmospheric pressure the measure obtained represents the effective distending force within the vessel when its surrounding medium is at a pressure of one atmosphere. The heart and the intra-thoracic portion of the great vessels are subjected to a sub-atmospheric pressure and therefore the (effective) distending pressure acting on the walls of these exceeds the manometric recording by an amount equal to that by which atmospheric pressure exceeds intra-thoracic pressure. Auricular
catheterisation fails to record this no less than peripheral vein puncture. In consequence of the fall in intra-thoracic pressure during inspiration (and during deep inspiration it may fall to -30 to -40 mm. Hg. (Wiggers, 1940)) the capacity of the intra-thoracic vessels and cardiac chambers becomes greater than this was during expiration and blood flows from the extra-thoracic veins to restore the balance of pressures (Hill and Barnard, 1897). The reverse occurs during expiration, but significant reflux into the veins is prevented by the existence of valves and, no doubt, by other means also for valves between auricle and venae cavae are lacking. In the phase of lowered intra-thoracic pressure, moreover, the capacity of the pulmonary vessels is increased and their resistance diminished (Hamilton, Woodbury and Vogt, 1939) so that pulmonary arterial and venous pressures are reduced at the same time as right auricular and peripheral venous pressures are reduced, effective venous pressure and right ventricular output increased, left ventricular output and systemic arterial pressure reduced. The reverse occurs when intra-thoracic pressure rises (Wiggers, 1940, Cournand, 1947).

There is a potential safeguard against the effects of excessively low and excessively high intra-thoracic pressures. Coincident with a diminishing intra-thoracic pressure the volume and velocity
of venous inflow increases; as the decrement of pressure energy is in direct proportion to velocity; venous pressure falls more rapidly as the blood courses towards the heart. If the rate of inflow becomes sufficiently rapid venous collapse must occur in consequence of the falling pressure. This will occur in extra-thoracic veins when the pressure within them is reduced to atmospheric; and it will naturally happen first in that part of the extra-thoracic venous system which is nearest the heart (this was demonstrated by Holt (1944) in animals; their veins collapsed just outside the chest—where, precisely, from a consideration of pressures they would be expected to do so). The collapsed segment of vein constitutes an obstruction to blood flow and hence protects the heart from a greater loading. The venous channels distal to the collapsed segment become distended and the pressure within them increases until the obstruction is overcome and venous inflow to the heart is resumed. When intra-thoracic pressure rises steeply the mounting auricular pressure coincides with a diminishing venous gradient and, therefore, a falling cardiac output. If this is progressive the stage comes when auricular pressure exceeds peripheral venous pressure and inflow ceases. The peripheral pressure rises in consequence until it becomes greater than auricular
pressure and venous inflow is restored. Richards (1945) has shown that in right heart failure auricular pressure is greater than peripheral venous pressure during most of the cardiac cycle and that "only at the time of initial ventricular contraction and again at the opening of the tricuspid valve is there a sharp drop in atrial pressure with rapid pouring in of blood from the overfilled great veins".

In the presence of emphysema intra-pleural pressure is uniformly raised and commonly fluctuates around that of the atmosphere (Kounts et al. 1929, 1932, 1934). Expiration is possible only by an active muscular effort producing a positive pleural pressure (Christie, 1934). The former authors chose to compare emphysema to a perpetual Valsalva experiment. They therefore regarded the raised pleural pressure as the cause of the venous hypertension that they consistently observed in this disease.

The positive intra-pleural pressure of emphysema is not comparable in degree to that obtaining in forced expiration against a closed glottis, and the evidence is against its being the direct cause of the raised venous pressure. When intra-thoracic pressure is raised experimentally as in the Valsalva experiment or in positive pressure breathing the auricular pressure, as stated, is increased more than is the pressure in the peripheral veins; the venous gradient is diminished and cardiac output
falls (Cournand, 1947), the whole being comparable to cardiac tamponade (Car and Essex, 1946). In these circumstances the velocity of blood flow in the peripheral venous segment must be retarded and the corresponding circulation time prolonged, for this reason: The distensibility of veins is such that the volume of blood contained by them (and therefore their cross-sectional area) is increased considerably, before the pressure within them begins significantly to rise (Starling, 1920; Blumgart, 1931). Hence, lessening of the velocity of blood blow, and therefore a longer circulation time, must precede increase in venous pressure. This argument is strictly relevant, for the only way that intra-thoracic pressure can affect the pressure in the peripheral veins is by causing a corresponding (though not equal) change of pressure within the right auricle. In emphysema (Tables VII and VIII) arm to tongue time is faster than in health (and arm to lung time is not prolonged) at the time when peripheral venous pressure is significantly increased. The co-existence, as here, of a fast circulation time is incompatible with a centrally produced increase in peripheral venous pressure. It cannot be therefore that the raised intra-pleural pressure of emphysema is alone the cause of the venous hypertension that occurs in this disease. Furthermore, in emphysema the cardiac output is raised (McMichael, 1946); accordingly the venous gradient and venous inflow must both be increased - which also is
incompatible with a centrally operative mechanism of the kind in question.

From a consideration of Piseuille's law in its application to blood flow in man (and in this respect it is strictly applicable within the limits mentioned above) it follows that the combination of raised pressure and unretarded blood flow in the peripheral venous channel must have its origin in the pre-venous part of the circulation; there must be a greater pressure remainder after the blood has overcome the resistance of the (systemic) arterioles, capillaries and venules, and this pre-supposes a greater diameter of individual units among these vessels. The arteriolar system constitutes by far the greatest part of the peripheral resistance; at this level the decrement of pressure is precipitous, exceeding quantitatively the total change throughout the remainder of the vascular system. By arteriolar dilatation, therefore, pressure energy available to the afferent side of the circulation could be increased with greatest mechanical efficiency.

The increase in lateral pressure in these circumstances, however, would be largely nullified by the greater cross-sectional area and reduced velocity of flow. Conservation of pressure (and of venous return) necessitates a diminished capacity in the venous channels; this mechanism would be maximally effective in the venules and smallest veins for their unre-
strained capacity is so much greater than that of more centrally placed veins. To this end a veno-constrictor mechanism exists (Hooker, 1921; McDowall, 1935; Mears, 1935, Doupe et al., 1939). Contraction of skeletal muscles, notwithstanding the tension that can be generated within them (Henderson, 1936), is of doubtful significance in this respect; blood flow is augmented however by descent of the diaphragm (Wiggers, 1947). Of the mechanism thus postulated for the venous hypertension arteriolar dilatation is calculated to reduce the velocity of flow and veno-constriction to increase it; the resultant will be a compromise between the two and is unlikely to differ markedly from the normal either way. The diminished cross-section of veins, moreover, will augment the venous gradient from the periphery to the heart. The consequently greater volume flow will contribute to increase both venous pressure and velocity of flow. The end result is as in emphysema. There is likely to be much more but this much is likely to be true.

Other potentially significant variables are blood viscosity, total blood volume, and the volume-elasticity pattern of the vascular system as a whole. It is reasonably assumed that hydrostatic pressure is constant and the ventricular rate of all patients with uncomplicated emphysema ranged from 70 to 90. The suggestion that the loss of pulmonary elasticity which constitutes emphysema is part of a generalised
degeneration of elastic tissue (Gibson, 1948) was not favoured by Kountz and Alexander (1934) and was refuted by Christie (1944). There is no reason to believe that such variation in total blood volume or viscosity as is likely to occur would detract from the augmentation of blood flow. No convincing information exists on total blood volume in uncomplicated emphysema although an increase, almost entirely due to erythrocytosis, is said to occur in congestive heart failure caused by emphysema (Meneely and Kallitreider, 1943; Richards, 1945). It has not at any time been suggested that blood volume is reduced. Polycythaemia was strikingly absent from patients in this series, even those with congestive heart failure, and there was no indication otherwise that blood viscosity differed appreciably from the normal. Although polycythaemia has proverbially been associated with emphysema its absence has previously been commented upon (McMichael, Sharpey-schafer and Howarth, 1947). Certainly the relationship between anoxaemia and polycythaemia is not a direct one (Harrop and Wintrobe, 1938). It is pertinent to remark in this connection that Taussig and Blalock (1947), in their investigation of congenital heart disease in children, found that oxygen arterial saturation as low as 65-70 per cent does not necessarily lead to polycythaemia and that, in fact, there is no need for compensatory
polycythaemia so long as oxygen saturation is above 66 per cent — a much lower level than a normal individual can tolerate.

The extent to which intra-thoracic pressure is raised by the experimental methods referred to correlates clearly with venous pressure increase but that does not necessarily imply that the former is the cause of the latter. There is more in these methods than positive pressure; anoxia of varying degree exists in most. Asphyxia has long been associated with venous distension and cyanosis. Apnoea is accompanied by a rising venous pressure which falls gradually when breathing is resumed. The same phasic variation occurs in the apnoea and hyperpnoea of Cheyne-Stokes breathing (Lyons et al., 1938). Kountz and Alexander (1934) produced anoxaemia in dogs and observed that venous pressure rose in proportion to the oxygen desaturation of arterial blood. The variations in venous pressure gradient and in cardiac output during positive and negative pressure breathing in dogs (Holt, 1944) were not produced when oxygen was substituted for air. Lennox and Gibbs (1932) observed a greater velocity of blood flow coincident with oxygen unsaturation caused by reducing oxygen tension in the alveolar air. Venous pressure can be raised in the same way. The association of venous hypertension and increased velocity of blood flow on the one hand with anoxia on the other is as real
as that of venous hypertension and decreased velocity of flow with raised intra-thoracic pressure.

Experimental anoxia in animals causes an increased diastolic volume of the heart and a greater systolic output (Stronghold, 1930). A high venous pressure and cardiac output characterise chronic anaemia (Richards and Strauss, 1928; Sharpay-Schafer, 1944) and recovery from acute haemorrhage (Wiggers, 1940). A short circulation time co-exists in both. These, however, are not strictly comparable in that the physiological pathology is a reduced oxygen content and blood volume is known to be reduced. At least in some cases of thyrotoxicosis, in which oxygen lack is relative rather than real, blood velocity and volume flow are increased in the same way. It can be predicted that corresponding changes occur in other circumstances of pure oxygen deficiency e.g. chronic carbon monoxide poisoning.

Peripheral vasodilatation and an increased venous pressure and inflow are part – the most important part – of the circulatory adaptation to prolonged anoxia. An increased cardiac output and velocity of flow are then inevitable. These circulatory changes are designed to effect oxygen/
saturation of a maximum quantity of arterial blood per unit time and thus a maximum oxygen availability to the tissues. They occur during acclimatisation to high altitudes (Sands and de Graff, 1925).

The physiological disadvantage of living at 1500 feet above sea level is inherent in the difference between an oxygen tension of 100 mm. Hg. and one of 50 mm. Hg. (approximately) which represents an oxygen saturation of 80-85 per cent. Notwithstanding the apparently minor unsaturation the disadvantage is a very real one to the individual who experiences it for the first time; during continued residence at this height the circulation becomes adapted compensatorily in the way that has been described. The diastolic size of the heart increases and its output becomes greater accordingly (Sands and de Graff, 1925; Stronghold, 1930; Grollman, 1932). Yet in emphysema not only does this degree of oxygen unsaturation occur (Meakins and Davies, 1925) but considerably greater unsaturation is common (Howarth, McMichael, and Sharpey-Schafer, 1947). The difference is that at the high altitude the oxygen in the inspired air is at a reduced pressure/
so that correspondingly less diffuses into the blood; in emphysema the inspired air is not qualitatively deficient but there is a diminution in effective ventilation (Christie, 1934). The end result is the same.

It can reasonably be argued from the facts enumerated that the dynamic quality of the circulation in the presence of emphysema is occasioned by oxygen lack and represents a compensatory adaptation calculated to ensure an optimum oxygen supply to the tissues in the most economical way.

Budd (1840) correlated enlargement of the right heart with increased capillary resistance in the lungs. Isaakssohn (1871) stressed the obliteration of small vessels in the emphysematous lung and considered that this, by increasing the resistance in the lesser circulation and imposing a strain on the right ventricle, eventually caused heart failure. This conception has been accepted and reiterated by numerous investigators since that time, and continues now to be the standard statement of pathogenesis of the heart failure of emphysema. None the less dissent from this theory has been implied, if not directly expressed, periodically from the time that it was first produced, largely for the reason that when enlargement of the heart was observed it affected both sides. This, in fact, had been Laennec's (1826) experience. Gairdner (1849) was the first forth-
right critic of the established view. He refused to believe that obstruction in the pulmonary circulation caused enlargement of the heart, substantially for the reason just mentioned. Kountz, Alexander and their co-workers (1927, 1929, 1933, 1934) strove hard to make known that the reputedly increased resistance in the pulmonary circulation does not exist in emphysematous lungs and, moreover, that emphysema does not usually affect the heart in any material way. When they did find any cardiac enlargement it was generalised, and enlargement of the right ventricle alone was excessively rare. Most writers, however, adhered to the orthodox view that the right heart is selectively enlarged due to the greater resistance in the lesser circulation, irrespective of how frequently such enlargement was demonstrable or how frequently enlargement of the left ventricle co-existed. The subject of cardiac enlargement will again be referred to presently.

Lichtheim (1876) concluded from animal experiments that about three-quarters of the total number of branches of the pulmonary artery require to be ligated before arterial pressures are affected in any way. These experiments have been repeated many times and the general experience has been that not until less than 40 per cent of the lumen of the pulmonary artery or the equivalent of all its branches remains does the pressure in the pulmonary circulation or the cardiac output change (Cohnheim, 1889; Moore and
Binger, 1927; Gibbon, Hopkinson and Churchill, 1932; White, 1945). Life is still compatible with occlusion of the artery up to 85 per cent of its sectional area. It has now been established that there is no permanent change of pressure in the right ventricle or pulmonary artery in man following ligation of one pulmonary artery as in pneumonectomy (Cournand, 1947).

The almost unlimited capacity of the pulmonary blood vessels and their spontaneous adaptation to greatly varying volume content has already been emphasised. It has been calculated that the blood content of the lungs under basal conditions ranges from 600 to 400 cc. or 11 to 8 per cent of the total blood volume (Blumgart and Weiss, 1928; Courmand, 1947); that it varies from 9 per cent to the total blood volume during inspiration to 6 per cent during expiration, and that it may amount to 20 per cent in circumstances still within the physiological range (Taylor and Best, 1945). Nylin (1947), by a technique involving temporary occlusion of the lung pedicle immediately prior to pneumonectomy and previous injection of "tagged" red blood corpuscles, found that the one lung in these particular circumstances contained 17 per cent of the total blood volume.

It has been estimated that not more than one twentieth of the total aerating surface of the lungs is used at rest (Drinker, 1946), and that dogs can
exercise without embarrassment after 50 per cent of lung tissue has been removed (Drastich, Adams, Hastings and Loupere, 1934). Finally, after pneumonectomy in children not only is there no permanent increase in pulmonary arterial pressure and no decrease in cardiac output but their ventilatory capacity is adequate for strenuous exercise and their oxygen saturation is not different from that of normal children under the same conditions (Lister, Courmand and Riley, 1942; Maier and Courmand, 1943; Courmand, 1947).

From these observations it follows that the obliteration of small vessels that does undoubtedly occur in emphysematous lungs is not of itself likely to impose an extra load on the right heart; the hypothesis that it does so (and it was never more than a hypothesis) does not accord with established facts concerning the dynamics of pulmonary blood flow. Courmand (1947), measuring ventricular pressure directly has shown that in emphysema of moderate degree there is no hypertension in the pulmonary arterial circulation and that only in those with most severe symptoms does the pulmonary arterial pressure rise.

The work of the heart is calculated as the sum of the work done in ejecting a certain volume of blood (i.e. cardiac output) against aortic (peripheral) pressure and that done in imparting velocity to the
aortic stream. It has been estimated (Remington and Hamilton, 1947; Hamilton, 1947) that the kinetic work is in the order of only 2 per cent of the total except in circumstances where the stroke volume is abnormally large and the diastolic pressure abnormally low. Although the kinetic part is usually discarded in the calculation of heart work under physiological conditions the relevant variations in emphysema will tend to its greater import. The increased velocity of circulatory flow which has been established as co-existing with emphysema is, at least in part, a reflection of the greater cardiac output which is known to characterise the disease (Fishberg, 1944; McMichael, 1946; Howarth, McMichael and Sharpay-Schafer, 1947). These in turn, in the absence of significant tachycardia as in the series now reported (vide supra), imply a greater stroke volume and, as is best observed in the uncomplicated disease, a raised pulse pressure. The conditions thus exist, according to Hamilton's criteria, where the kinetic work of the heart becomes an appreciable part of the whole. Irrespective of that, however, the "pressure" work of the heart is increased by reason of its greater output without, necessarily, any increase in pressure. It would accord with biological adaptation if this extra burden of work were borne by the heart with a maximum economy of oxygen, and it is so. It has been shown in the intact heart and heart-lung preparation that when the work of the heart is increased by
reason of an increased inflow (which is the governor of output) proportionately less oxygen is consumed by the heart and its efficiency is increased accordingly (Landowne and Katz, 1944). If the same increment of work were effected by an increased resistance the oxygen consumption by the heart would be greater. In addition to this higher level of metabolism the hypertensive heart reaches the limit of its performance earlier than does the heart equally loaded by an increased venous inflow (Landowne et al., 1944).

An inevitable accompaniment of a greater systolic ejection is a greater diastolic distension of the ventricle (Starling, 1918; Wiggers, 1940) and this in turn implies a greater residue of blood in the heart at the end of systole (Green, 1944). Within a comprehensive range of ventricular rate, therefore, the heart must be enlarged dynamically from the time that its output increases. This constitutes enlargement in a radiological sense so long as it is sufficiently pronounced to be recognisable. Anatomical characteristics of the heart might well determine its first being manifest in the pulmonary artery and conus. This happens in other circumstances where the heart is dynamically over-active as in thyrotoxicosis and chronic anaemia. Parkinson and Hoyle (1937) found that the part the heart next to be recognisably enlarged in emphysema was the outflow tract of the right ventricle. It was the experience of Robb and Steinberg (1939)
that both inflow and outflow tracts were enlarged to the same extent.

In the competent heart, apart from the brief interval of time lapsing before one ventricle adapts its output to a change in the output of the other, the output of both ventricles is equal. An increase in output therefore will proportionately increase the work of each. Continuing this argument, when enlargement of the heart exists as a consequence of emphysema the enlargement must affect both sides of the heart. If it is not so, and the discrepancy is not due to the observer's error (or his predilections), then there must be another cause. Heart failure is one such cause.

Although the popular view has always been that emphysema causes selective enlargement of the right heart there is, none the less, nothing novel in the suggestion that this is not so but that the heart enlarges as a whole. On the basis of post-mortem, clinical and radiological observations it had previously been contended that enlargement of the heart was rare in this disease but that in the minority where enlargement was recognisable it was generalised (Gairdner, 1849; Peacock, 1855; Waters, 1860; Johnson 1868; Jenner, 1871; Greenhow, 1873; Hoover, 1913, 1928; Kountz et al., 1927, 1929, 1934; Podkaminsky, 1929, 1930).
It has been said that under no circumstances does uncomplicated emphysema cause structural enlargement of the heart (Rubin, 1936; Kerley, 1938). Parkinson and Hoyle (1937), in a predominantly radiological investigation of 80 cases of advanced emphysema of whom 13 were in congestive heart failure, found no demonstrable enlargement of the heart in one third of these and great enlargement of the right heart in only four; enlargement of the pulmonary artery or conus in 56 per cent of the whole, and enlargement of the left ventricle in 30 per cent. They attributed the left heart involvement to co-existing cardio-vascular disease of other etiology which they found in half the total. Parker (1940), after exclusion of all other possible causes of heart disease, found enlargement of the left ventricle in 34 per cent of emphysematous patients. The frequency of left ventricular enlargement in emphysema has always earned much comment notwithstanding the dominant appeal of right heart enlargement (Laennec, 1826; Sibson, 1848; Criep, 1932; MacDonald; 1932; Scott and Garvin, 1941; Fishberg, 1944).

In contrast to the dynamic compensatory mechanisms that constitute the emergency reserve of the circulation cardiac hypertrophy needs greater time for its development. There is little factual knowledge concerning the precise stimulus that leads to hyper-
trophv. While a correlation exists between many circulatory faults and hypertrophy of the heart there is no proof that any of them is necessarily the cause of it; on the other hand an association that does not conform to predetermined concepts is as likely to be branded as inconvenience as a correlation. When the work of the heart has been in excess of its natural amount over a prolonged and continuous period of time the myocardium is usually hypertrophied.

Increased work alone does not cause the heart to fail but a limit is set to the functional value of hypertrophy by reason of the fact that the capillaries of the coronary circulation do not increase in proportion. (Shepley, Shepley and Wearn, 1937). Relative ischaemia of the myocardium therefore ensues and a potential cause of failure exists. Further, selective right ventricular strain occurs at the late stage of the disease when pulmonary arterial pressure rises (Cournand, 1947). Congestive heart failure can, and does, occur as a direct consequence of emphysema. Irrespective of the reason why, that failure is selectively or dominantly of the right ventricle

When heart failure occurs in emphysema it occurs in a circulation that is already characterised by a high venous pressure and a fast rate of blood flow. The changes in circulatory dynamics that constitute heart failure must therefore be superim-
posed on these. Slowing of the circulation is an inevitability in congestive heart failure from any cause (Fishberg et al., 1933), but that slowing is relative to its velocity before the heart failed. If, in the course of emphysema, arm to lung (and, therefore, arm to tongue) time becomes recognizably prolonged then, in the absence of other cause which will be obvious, the heart is failing although the circulation times may still be within normal limits. In the latter event the existence of prolonged circulation times can only be appreciated by a comparison of serial records.

A significant prolongation of arm to tongue and arm to lung times was demonstrated in every patient in the group of emphysema heart failure (Table IX). In all but three of these it was possible (if necessary) to do this at a single recording when they came under this specialised observation because their circulation times exceeded the corresponding maximum recorded in the controls. Of the three exceptions it was necessary in one (Case 54) to measure circulation times from the wrist, not the antecubital space (for reasons that have already been given). The circulation times concerned, therefore, are not comparable with any control figures (although lung to tongue time is). In the other two (Cases 51 and 56), although arm to tongue time in each case was just greater than the corresponding maximum in the controls,
arm to lung time was within the control range. These three patients, however, had been under hospital care before and their circulation times had been recorded from time to time during the previous eighteen months. Relative to these the increase in both arm to lung and arm to tongue times was apparent. This includes the patient whose circulation times were measured from the wrist for they had always been so; comparison with previous wrist to tongue and wrist to lung times is therefore valid and has the same significance as if they were measured from an antecubital vein.

In all, moreover, who recovered from heart failure or improved temporarily arm to tongue and arm to lung times diminished in proportion (Table X).

Of the 40 patients in the group of uncomplicated emphysema (Table VII) eight had peripheral oedema at the time they were admitted to hospital, yet in none of these nor of the 32 without oedema did any of the segmental circulation times exceed the values recorded in the controls. By ordinary clinical standards the patients who did have oedema might have been diagnosed as cor pulmonale but serial observations in all of them failed to reveal any increase in either arm to lung or arm to tongue time coincident with the aggravation of symptoms and the occurrence of oedema. One or more previous records of circulation times from each patient was available
for comparison. As their clinical condition improved and the oedema disappeared their circulation times did not diminish as would be expected if they had had congestive heart failure. On the contrary, in these patients circulation times tended to become longer as they recovered. In five of them (Cases 16, 18, 26, 27 and 36) the increase in arm to tongue time was appreciable; in the other three (Cases 14, 25 and 33) the variation was probably not significant either way.

The usual cause of the deterioration that brings the emphysematous patient to hospital is an acute exacerbation of bronchitis. This applies whether or not he presents with heart failure. The tentative interpretation of the lengthening circulation times during recovery is that the addition of an acute respiratory illness impairs still further the respiratory capacity of the emphysematous lungs and so necessitates a faster circulation of blood in the attempt to preserve the previous oxygen availability to the tissues. Should the constancy of this change in circulation time in these circumstances be established it means that the physiological defect is a respiratory one; there cannot be failure of a heart and circulation that react by increased activity designed to compensate for that defect - irrespective of the presence of oedema, distended neck veins and much else
that is included in the symptomatology of heart failure. On the other hand, in disease that conforms clinically to emphysema with heart failure, if with clinical improvement circulation time diminishes then that disease is congestive heart failure (whether it is due to emphysema or not).

More evidence will presently be adduced in further support of this interpretation of cardio-pulmonary dynamics in emphysema and especially of the view that oedema may be caused by emphysema alone. Meantime it may be mentioned/the combination of anoxia and high venous (and capillary) pressure is itself sufficient to account for the oedema and is, coincidentally, the same as that to which cardiac oedema is usually attributed (Landis, 1925, 1927, 1928; Volhard, 1931, Krogh, Landis and Turner, 1932). Anoxia is in all circumstances a most potent influence in the production of oedema and it is doubtful if increase in capillary pressure alone is ever responsible (Drinker, 1946). Kountz and Alexander (1929, 1934) have reported emphysematous patients with high venous pressure and oedema in whom they could find no evidence of heart disease either clinically or at autopsy.

If therefore, as is contended, dyspnoea on effort, cyanosis, venous hypertension and peripheral oedema can occur with emphysema in the absence of heart failure recognition of the heart failure of emphysema
becomes increasingly difficult. It is rarely that the diagnosis can be established, as is maintained (Durant, 1946), by the presence of venous engorgement of the liver. Engorgement of the liver is ordinarily presumed from enlargement of this organ in circumstances conducive to venous stasis - so long as no gross change in the consistency or outline of this organ suggests another cause for its enlargement. It is only in exceptional heart failure (and then advanced and easily diagnosable by more direct means) that hepatic venous engorgement can be indentified as such by the quality of the pulsation transmitted to the palpating hand. Moreover the size of the liver is equated clinically with the level of its lower margin, established by palpation or percussion, and enlargement is inferred in proportion as this level is below the costal margin. More in the realm of text-books than in clinical practice the inference is confirmed by percussing the upper limit of the organ and defining its level on the surface - an undertaking of dubious value if only because the upper surface of the liver is curved and lung and pleura intervene between it and the chest wall. The degree of curvature and the amount of lung intervening vary with the physical configuration of the individual. In the emphysematous patient, by reason of the inspirational position of the lungs, the higher intra-pleural pressure and the descent of the diaphragm, the liver is displaced to a lower
level. If the chest is barrel-shaped and the costal margin therefore splayed the downward displacement will be, relatively, greater. In the presence of hydrothorax (which may succeed congestive heart failure of varying etiology, including emphysema) the displacement is greater still, and the upper border is certainly indefinable clinically. Obesity alone may preclude manual palpation of the lower margin of the liver and cause "liver dullness" to bear little relationship to its true anatomical outline. Finally, an organ enlarging generally will enlarge maximally in the direction of least resistance which does not necessarily include the palpable antero-inferior edge, nor a part whose enlargement can be recognized by a sufficient alteration in sound when the thoracic or abdominal wall over it is percussed. For these reasons clinical evaluation of hepatic engorgement is not a valid practical test of heart failure supervening on emphysema.

Nor will electrocardiographic (Parkinson and Hoyle, 1937; White, 1945) or X-ray examination (Parkinson et al., 1937; Kerley, 1938) establish that diagnosis when it is clinically in doubt.

Statistically, peripheral venous pressure in emphysema heart failure is greater than in uncomplicated emphysema (Table X) but in the individual it may not be so (Table VII and IX). Hence, although a
rising venous pressure is an invariable accompaniment of congestive heart failure (Lewis, 1930; Fishberg, 1944) a pressure in excess of normal (Table VI) lacks any significance in the emphysematous patient unless it also exceeds the range of raised pressure due to emphysema alone. In the advanced stages of emphysema heart failure it probably always does; in the early stage it commonly does not.

It has long been known that manual compression of the engorged liver in the patient with congestive heart failure causes visible distension of the superficial jugular veins (Pasteur, 1885; Randot, 1898). More recently it has been shown that in the presence of right ventricular failure compression of the liver (Hitzig, 1942), the right upper quadrant of the abdomen (Winsor et al., 1946) produces an increase in brachial venous pressure. In the intact circulation the same compression causes the pressure to fall slightly or produces no change (Winsor et al., 1946).

This test was applied to every individual included in the present investigation. In the controls (Table VI) and in all patients otherwise diagnosed as uncomplicated emphysema (Table VII) abdominal compression caused no appreciable change in brachial venous pressure. This includes the eight patients who were considered not to have heart failure because their circulation times were unprolonged, notwith-
standing that they had obvious oedema at the same time. In all classified as emphysema heart failure by other standards (Table IX) brachial venous pressure rose abruptly when the abdomen was compressed and the increase in pressure was so pronounced as never to be equivocal. The implication is that a positive venous pressure response of this kind is a sign of right failure when the mere recording of peripheral venous pressure or the inspection of neck veins may be misleading. Conversely, the absence of this response, so long as there is no unrelated obstructive lesion in the venous pathway concerned, is exclusive of right heart failure.

In the emphysematous patient with high venous pressure, peripheral oedema and circulation time within the normal range, the most comprehensive single clinical examination will not differentiate simple emphysema from the right heart failure that it may give rise to. The technical requirement for the diagnosis of right heart failure is the demonstration of (relative) circulatory stagnation in the systemic venous channels or of failure by the heart promptly to increase its output as its inflow is increased. A positive venous pressure response to abdominal compression is probably a demonstration of both. In the present series the differentiation of emphysema and right heart failure obtained by this test agrees in detail with that made on the basis of serial circulation times.
That the "normal" response occurs in emphysema, even in the presence of obvious oedema, necessarily implies that different mechanisms underlie the permanently raised venous pressure of emphysema and that of right heart failure. From the previous consideration of these pressures it follows that whereas in uncomplicated emphysema the increase in peripheral venous pressure is actively determined (as by veno-constriction) in right heart failure the increase, though not necessarily the whole increase, represents a passive response to a raised auricular pressure. (The sequence of dynamic changes concerned has already been discussed in detail). This statement is made in the awareness that active compensatory changes do occur to alter the dynamic quality of the circulation in heart failure and that one effect of these will be to submerge the increment of venous pressure that has been produced as indicated. The passive pressure phenomenon has its equivalent in a retarded blood flow, the active in an accelerated flow. The presumption is that the amount by which brachial venous pressure increases when the abdomen (or liver) is compressed represents the increment of pressure that is passively determined.

This concept of different qualities of venous hypertension based on simple hydraulic principles is corroborated by a comparison of circulatory dynamics in congestive heart failure of varying etiology. That arm to tongue and arm to lung times
are approximately twice as long in rheumatic heart failure as they are in emphysema heart failure (Tables XII and XIII), notwithstanding that venous pressure is equally elevated in the two, conforms to the previous contention that the velocity of venous blood flow varies with the diameter of the veins rather than with the pressure within them, and confirms the deduction, arrived at otherwise, that a venoconstrictive influence is not only operative in emphysema but persists when this gives rise to congestive heart failure. It does not, on the other hand, imply that venoconstriction may not also occur in heart failure of rheumatic or other etiology but merely that the total increase in venous pressure found in these is not determined by venoconstriction alone nor by other active mechanisms, as it is in (uncomplicated) emphysema.

Irrespective of shortcomings in the theory of "backward pressure" in explaining the indentifiable venous congestion of right heart failure and of merit in the negation of that theory (McMichael, 1938, 1946; Starr, Jeffers and Meade, 1943; Warren and Steade, 1944), an inevitable immediate consequence of "failure" of a ventricle is an increase of pressure in the auricle that serves it. Venous inflow is in turn retarded and peripheral venous pressure increased, notwithstanding that these quantitative changes may not, for the reason stated, be recognisable as such.
As failure advances so auricular pressure rises but peripheral venous pressure does not (as shown above) on rise by equal amount and therefore the venous gradient falls. A logical development of this argument is that a time will come in the failure of the heart when auricular pressure exceeds peripheral pressure and inflow ceases. This, in the continuance of life, cannot be but temporary for it is self-limiting; the absence of inflow must cause a prompt increase in peripheral venous pressure which, when it exceeds auricular pressure, re-establishes the venous gradient and auricular filling is resumed. The test of the argument is its fulfilment. It has now been shown by direct measurement that in advanced cardiac failure auricular pressure exceeds peripheral venous pressure during the greater part of the cardiac cycle (Richards, 1945).

The compensatory reactions to a failing circulation, which have been referred to frequently, include veno-constriction (Donagan, 1921; Gollwitzer-Meier, 1930, 1931; McMichael, 1938) and an increase in circulating blood volume. The latter is known to exist in the presence of congestive heart failure and to diminish with improvement although there is a lack of knowledge concerning the stage at which it develops and the precise stimulus that leads to it (Lorrain Smith, 1902; Twig and Hinsberg, 1930;
Wollheim, 1931; Gibson and Evans, 1937; Meneely and Kaltreider, 1943; Warren et al., 1944; Fishberg, 1944; Nylin, 1947). By reason of the volume elasticity ratio throughout the vascular system (Green, 1944) both these mechanisms will act in the direction of increasing venous pressure, velocity of blood flow and auricular filling pressure. So long as the heart is capable of responding to a greater venous inflow its output will be increased. The same mechanisms will tend therefore to neutralise the retardation of blood flow and to augment the venous hypertension which are the pure consequences of heart failure. Although the distensibility of veins is so great that a moderate increase in circulating blood volume would of itself cause little change in venous pressure in the intact circulation (Plumier, 1909; Fyster and Middleton, 1924; Villaret, Saint-Girons and Justin-Besanson, 1930; Richards, Caughey et al., 1937; Landis, Brown, Fauteux and Wise, 1946), it would be otherwise in a previously distended venous system (Starling, 1920) — which is inevitable in the evolution of congestive heart failure as postulated in this thesis. Furthermore, it has already been made clear that absolute measurements of either central or peripheral venous pressures, considered as isolated observations, are not necessarily indices of venous inflow or cardiac output.
The view has been expressed that contraction of veins may act by damming back blood, thus preventing its return to the heart (Pogany, 1931; Bauer, Dale, Poulsson and Richards, 1932) but, irrespective of whether this is or is not true, clearly there are circumstances in the course of some forms of congestive heart failure when such would be advantageous.

The active measures that comprise circulatory adaptation to heart failure are in the main equivalent to those determined by anoxia (vide supra) and therefore are not exclusive to cardiac failure. It has been shown that corresponding changes, though not necessarily all, occur in emphysema. It only remains to add that in the latter also there is a lack of unanimity on variation in blood volume. An increase was recorded by Plesch (1922), Uhlenbruck (1931) and, exceptionally, by Fishberg (1944), but Kaltreider, Hurtado and Brooks (1934) found no change in plasma or red cell volume. The vagaries of reported red cell content have been referred to Price-Jones (1921) maintained that the characteristic change was not polycythaemia but an increase in corpuscular volume and red cell diameter. Lemon (1929) was unable to confirm this but found an increase in corpuscular haemoglobin. It is probable that circulating blood volume varies largely with corpuscular content. Polycythaemia is only one part of the compensatory reaction and certainly not a dominant one (Taussig and Blalock, 1946). The whole reaction is a blend of variables, the contribution of each probably
governed by quantitative stimuli and designed to produce a maximum efficiency of the whole. The change in the milieu of the bone marrow that constitutes, in the presence of anoxia, the stimulus to red cell proliferation is as yet undetermined.

There are none who will now seriously dispute that in the classical form of heart failure directly due to emphysema the right ventricle fails primarily or dominantly (Kountz et al., 1936). There is less accord over the precise causation of that heart failure when it occurs.

Pulmonary arterial Hypertension occurs only in the advanced stage of emphysema (Courmand, 1947). If it is only in severest emphysema that heart failure occurs (and it is said that even then it does so only rarely (White and Brenner, 1933; Parkinson and Hoyle, 1937; Durant, 1946)) the additional handicap thus imposed on the right ventricle may, other things being favourable, lead to its selective failure. The reduction of vital capacity in severe emphysema is of a degree comparable to that of congestive heart failure from other causes and the symptom of dyspnoea on effort is equally prominent. The emphysematous patients however is not orthopnoeic and rarely becomes so in heart failure. Presumably the disadvantage of the active pulmonary congestion and diminished vital capacity implied in recumbency (Hamilton and Morgan, 1932) is equalled or exceeded by the advantage, on the oxygen debit side, of a greater cardiac output -
so long as this circulatory reaction to recumbency prevails.

In many cases of emphysema the further reduction in vital capacity inseparable from the passive pulmonary congestion of left ventricular failure would be incompatible with life (Blumgart and Weise 1927). None the less crepitations are commonly heard over the lungs of emphysematous patients in heart failure and not in its terminal stages only. Crepitations (in the sense in which the word is now used) are usually interpreted as moist sounds and, in the presence of heart failure, attributed to pulmonary oedema. They have been heard in patients of the kind referred to who have subsequently recovered. It is surprising that any individual recovers from pulmonary oedema (Drinker, 1946). It is most improbable that the patient with high grade emphysema will do so. For this reason alone it is considered that these "moist sounds" are not due to failure of the left ventricle. In the latter also lung to tongue time is invariably prolonged and vital capacity reduced, both to a considerable degree. In emphysema, under the circumstances referred to, lung to tongue time is within normal limits. The further reduction in vital capacity of emphysematous patients who develop heart failure, including those with "moist sounds", is relatively small, and so is the increase that occurs with recovery from heart failure. It bears no relationship to
clinical improvement. The reverse applies to left ventricular failure.

The most potent single factor in the production of pulmonary oedema in all circumstances is anoxia (Drinker, 1946). If the "moist sounds" of emphysema do indicate the presence of pulmonary oedema it may be caused in this way (at least in part), but it has already been suggested that the usual asphyxiating intra-alveolar oedema is incompatible with life in the presence of the severe emphysema. Parker and Weiss (1936) and Plotz (1939) maintain that a second variety of pulmonary oedema may occur, involving the respiratory tissue without transudation of fluid into the intra-alveolar spaces (Parker and Weiss, 1936; Plotz, 1939), but if peri-capillary oedema of this kind is, as it is stated to be, characterised by paroxysmal dyspnoea and the absence of crepitations it does not occur in emphysema, except, perhaps, terminally. The "moist sounds" referred to cannot be equated with pulmonary oedema so far as this is at present understood.

Acute left ventricular failure (following massive myocardial infarction) did supervene on the typical heart of emphysema in one of the patients in this series and he quickly died (Table IX), (Case 60). In the interval he became orthopnoeic and his lung to tongue time increased from 5.4 to 16.5 seconds
but no attempt was made to record his vital capacity which previously had been 35 per cent of its calculated normal value. It did not, however, appreciably exceed his tidal air. A second, previously known (Case 62) emphysematous patient had, when admitted, advanced right heart failure but the left heart failed additionally (although not acutely like the other) during the succeeding 24 hours. Though not originally orthopneic he became so before he died soon afterwards, his lung to tongue time in the meantime increasing from 5.5 to 11.0 seconds. The history indicated that this patient had had a fairly severe respiratory infection for at least 10 days and autopsy revealed that he had coronary arterial disease as well. His vital capacity was not recorded. A third (Case 56) probably had failure of the whole heart from the time of his admission to hospital and, in retrospect, it is questionable if he should have been included in the series. Although he too was known of old as having advanced emphysema he also had moderate systemic hypertension. In the past his symptoms had appeared to be determined by emphysema alone and when first seen in congestive heart failure this was assessed — but not without hesitation — as a direct consequence of emphysema. This was the only patient who was orthopneic when admitted to hospital and the only one who had auricular fibrillation. His lung to tongue time was 13.1 seconds (the
mean for all patients with emphysema heart failure was 6.83 seconds) and his vital capacity 20 per cent of its calculated normal value. He recovered. The three patients just described had crepitations, presumably caused by left ventricular failure, but other emphysematous patients with selective right heart failure had equally pronounced crepitations certainly not caused in the same way.

Heart failure may occur in emphysema for two reasons:-

(1) Either because of increasing emphysema alone or of added acute respiratory infection the heart, functioning maximally, cannot, in combination with the diseased lungs, maintain the minimum oxygenation necessary for its own integrity at that level of work. Anything that increases the metabolism of the individual will accentuate the oxygen deficiency. The primary failure is a ventilatory-respiratory one; other organs, including the heart, fail secondarily as their minimum oxygen requirement fails to be met. Whatever heart failure may be its overt development coincides in time with the stage at which an irreducible level of metabolism co-exists with a maximum availability of oxygen.

(2) The heart may fail at a time when emphysema has not advanced to the extent indicated in the first, with or without superimposed respiratory infection,
due to coincidental cardiovascular disease not normally correlated etiologically with emphysema. This is most commonly coronary atheroma, systemic hypertension or the two combined. The apparently frequent association of these with emphysema merits further investigation for it is likely to be more than fortuitous.

 Probably in all circumstances leading the chronic heart failure many noxious influences act to limit the heart's efficiency before it finally fails, although the apparent cause may only be the final increment of stress. Each one preceding it has contributed to reduce the dynamic reserve of the heart and anyone of these might happen to be the final injury that precipitates it into failure. In theory one would expect compensatory hypertrophy of the heart to be an ideal adaptation, limited only by anatomical confines. It is not so because the coronary capillary system does not expand in proportion and the myocardium becomes relatively ischaemic in consequence (Shepley, Shepley and Weary, 1937). Presumably the limit thus set to the biological value of cardiac hypertrophy serves some purpose; its disadvantage is that with a continued stimulus to hypertrophy the myocardium will ultimately fail. Given an equal increment of load for each side of the heart and assuming that each side hypertrophies in consequence of and in proportion to this increment it does not
follow that all parts of the heart will suffer equally or proportionally. Our limited knowledge of the minute capillary distribution in the myocardium of the various chambers does not permit prediction of unequal or equal effects of a relative ischaemia brought about in this way. It may be that in emphysema of moderate degree the relative ischaemia of cardiac hypertrophy facilitates differential failure of the right ventricle as pulmonary hypertension does at a later stage. The (absolute) myocardial ischaemia of coronary occlusive disease, on the other hand, usually causes selective failure of the left ventricle or affects the whole heart, as does systemic hypertension. So it is when these complicate emphysema.

The infrequency of auricular fibrillation in the heart failure of emphysema may (or may not) indicate their frequency as a cause. Ordinarily orthopnoea correlates with a prolonged lung to tongue time and both are indices of left heart failure. The correlation is unchanged in the presence of emphysema and the significance is the same, irrespective of whether or not right heart failure exists at the same time.

It would appear that the nearer the syndrome approaches that of pure right heart failure the more likely is it to be caused by emphysema alone.

The two categories of heart failure in emphysema may, for convenience, be referred to as anoxic and incidental heart failure. In both, according to the
dynamic principles considered to apply, cardiac output must be reduced relative to what it was immediately prior to failure, although it may still exceed a normal value. In the same way circulation time, though still brief, is prolonged, and such prolongation was, not so long ago, considered to be a more sensitive index of a falling cardiac output than its direct measurement by the method current at that time (Fishberg, Hitzig and King, 1933). It is known that the results obtained by that same method (Grollman, 1932) do not differ greatly from those obtained by the method in popular use at the present time (Fick, 1870; Baumann and Grollman, 1930; McGuire, Hauenstein and Shore, 1937; McMichael, 1932, 1938, 1944).
SUMMARY

(1) Fifty-two patients with pulmonary emphysema including twelve in congestive heart failure have been investigated with special reference to circulation times and peripheral venous pressure. Corresponding records were made in fifty healthy controls of comparable age.

(2) The evolution of the modern concept of emphysema, based on a historical review of the disease, is outlined. The etiology and pathology are discussed in so far as these are relevant to the main thesis. Emphasis is placed on the loss of elasticity by the lungs which is the salient lesion of emphysema and on the spirometric pattern of breathing which reflects pulmonary inelasticity.

Clinical recognition of emphysema is not nearly so simple as it is reputed to be. Throughout this investigation the diagnosis was based ultimately on spirometry - perhaps the only means by which the disease can be consistently diagnosed.

(3) The technical procedures of recording segmental circulation times and peripheral venous pressure are reviewed and the validity of current methods discussed in detail.

Notwithstanding the complexity of the cardiovascular system of man the circulation of blood conforms basically to physical laws. By the application of these an attempt is made to interpret circulation
times and peripheral venous pressure in so far as they reflect the dynamic quality of the circulation as a whole and the pulmonary circulation in particular.

(4) The recorded figures for arm to tongue, arm to lung and lung to tongue times and peripheral venous pressure in each of the three groups - controls, uncomplicated emphysema and emphysema with heart failure - are analysed statistically. The difference in venous pressure and corresponding segmental circulation times between (a) controls and uncomplicated emphysema, (b) controls and emphysema heart failure and (c) uncomplicated emphysema and emphysema heart failure is calculated and tests of significance applied. Supplementarily, the heart failure of emphysema is contrasted with rheumatic heart failure in terms of the same variants.

(5) In the presence of uncomplicated emphysema lung to tongue and arm to tongue times are significantly less than in the controls and venous pressure is higher. Arm to lung time does not differ significantly in the two groups.

(6) Irrespective of cause congestive heart failure implies a retardation of blood flow, and the heart failure of emphysema is no exception. Arm to lung and arm to tongue times are invariably prolonged relative to what these were in the emphysematous individual before the heart failed. Statistically, the same segmental circulation times exceed those of the
healthy controls but in the individual patient this is not necessarily so. The longer circulation times can then be recognized only by a comparison of serial records.

(7) Peripheral venous pressure is, statistically, higher in emphysema heart failure than it is in emphysema not so complicated but a given pressure, though obviously raised, will not necessarily differentiate between the two. The increased brachial venous pressure of heart failure may however be distinguishable by the further increase that can be caused by pressing on the abdomen with the hand.

(8) The symptomatology of emphysema (in the absence of heart failure) includes effort dyspnoea, cyanosis, distension of neck veins and, not infrequently, peripheral oedema. Recognition of congestive heart failure, therefore, when this supervenes on emphysema may be difficult if not, by ordinary diagnostic methods, impossible. Reasons are given why palpatory examination of the liver loses much of its value as a clinical test in the presence of emphysema. Neither by cardiographic nor by X-ray examination can a diagnosis be established. In these circumstances circulation times are, as a rule, within the normal range, but a significant prolongation of arm to lung (and arm to tongue) time, recognisable only by serial records, is considered to be diagnostic of right heart failure. The only other clinical test
likely to give the same information is an increase in brachial venous pressure produced by manual compression of the abdomen.

The variation in circulatory dynamics underlying the qualitative difference between the venous hypertension of emphysema and that of right heart failure is discussed at length.

(9) A prolonged lung to tongue time is ordinarily an index of left heart failure and there is every reason to believe that it means the same in the presence of emphysema, irrespective of whether or not right heart failure exists at the same time. In either case it implies additionally that the heart failure is not caused by emphysema alone. Orthopnoea, which correlates with a prolonged lung to tongue time, appears to have the same significance.

(10) Arm to tongue time is twice as long in rheumatic heart failure as it is in emphysema heart failure, notwithstanding that peripheral venous pressure is equally raised in both. In rheumatic heart failure also arm to lung and lung to tongue times are prolonged in proportion as the failure is dominantly of the right side of the heart or the left. In emphysema heart failure only arm to lung time is prolonged beyond normal values and, even so, it is scarcely more than half the corresponding time in rheumatic heart failure.
Emphysema is regarded as a ventilatory defect and the natural termination of progressive emphysema as ventilatory-respiratory failure. The accompanying cardio-vascular changes are compensatory and, as such, actively determined. The stimulus to this end is, probably, the complex influence of anoxia on internal environment.

The organ systems represented by heart and lungs are usefully regarded as a physiological unity.
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