Acute respiratory failure with increasing anoxaemia, hypercapnia, and acidaemia is responsible for the distinctive clinical picture observed during exacerbation of infection in the chronic bronchitic and emphysematous subject: headache, raised intracranial pressure, papilloedema, mental confusion, hallucinations, sweating, myoclonic jerking, increased cardiac output, pulmonary hypertension, and congestive cardiac failure.

Mortality from "bronchitis" has not declined in the last 10 years despite antibiotic therapy: respiratory failure may be a partial explanation of this phenomenon.

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REFERENCES

- Baldwin, E. de F., Courmand, A., and Richards, D. W. (1949). *Medicine*, Baltimore, 28, 201.
 Barach, A. L. (1948). *Physiologic Therapy in Respiratory Diseases*, 2nd ed. Lippincott, Philadelphia.
 — and Woodwell, M. N. (1921). *Arch. intern. Med.*, 28, 394.
 Binger, C. A. L. (1928-9). *J. clin. Invest.*, 6, 203.
 — Hastings, A. B., and Sendroy, J. (1927). *J. exp. Med.*, 45, 1081.
 Boutouline-Young, H. J., and Whittenberger, J. L. (1951). *J. clin. Invest.*, 30, 838.
 Callaway, J. J., and McKusick, V. A. (1951). *New Engl. J. Med.*, 245, 9.
 Donald, I. (1954). *Lancet*, 1, 895.
 Drinker, C. K. (1945). *Pulmonary Oedema and Inflammation*. Harvard Univ. Press, Cambridge, Mass.
 Elmes, P. C., Knox, K., and Fletcher, C. M. (1953). *Lancet*, 2, 903.
 von Euler, U. S., and Liljestrand, G. (1946). *Acta physiol. scand.*, 12, 301.
 Fenn, W. O., Rahn, H., and Otis, A. B. (1946). *Amer. J. Physiol.*, 146, 637.
 Hastings, A. B., Neill, J. M., Morgan, H. J., and Binger, C. A. L. (1924). *J. clin. Invest.*, 1, 25.
 Ivy, J. H., Grodins, F. S., Adler, H. F., and Snapp, F. E. (1947). *J. Aviat. Med.*, 18, 577.
 Lange, K., Craig, F., Tchertkoff, V., Oberman, J., and LoCasto, F. (1951). *Amer. J. med. Sci.*, 222, 61.
 Logan, W. P. D. (1953). *Lancet*, 1, 336.
 Lovejoy, F. W., Yu, P. N. G., Nye, R. E., Joos, H. A., and Simpson, J. H. (1954). *Amer. J. Med.*, 16, 4.
 McMichael, J., and Sharpey-Schafer, E. P. (1944). *Quart. J. Med.*, 13, 123.
 May, J. R. (1953). *Lancet*, 2, 899.
 Meakins, J. C., and Davies, H. W. (1925). *Respiratory Function in Disease*. Oliver and Boyd, Edinburgh.
 Mills, N. J. (1953). *J. Physiol., Lond.*, 122, 66.
 Motley, H. L., Courmand, A., Werko, L., Himmelstein, A., and Dresdale, D. (1947). *Amer. J. Physiol.*, 150, 315.
 Mulder, J., Goslings, W. R. O., van der Plas, M. C., and Cardozo, P. L. (1952). *Acta med. scand.*, 143, 32.
 Newburgh, L. H., Means, J. H., and Porter, W. T. (1916). *J. exp. Med.*, 24, 583.
 Patterson, J. L., Heyman, A., and Duke, T. W. (1952). *Amer. J. Med.*, 12, 382.
 Peters, J. P., Bulger, H. A., and Eisenman, A. J. (1925). *J. clin. Invest.*, 3, 511.
 Platts, M. M. (1953). *Clin. Sci.*, 12, 63.
 Prime, F., and Westlake, E. K. (1954). *Clin. Sci.*, 13, 321.
 Rosenthal, T. B. (1948). *J. biol. Chem.*, 173, 25.
 Scott, R. W. (1920). *Arch. intern. Med.*, 26, 544.
 Simpson, T. (1954). *British Medical Journal*, 1, 297.
 Stone, D. J., Schwartz, A., Newman, W., Feltman, J. A., and Lovelock, F. J. (1953). *Amer. J. Med.*, 14, 14.
 Taquini, A. C., Fasciolo, J. C., Suarez, J. R. E., and Chiodi, H. (1948). *Arch. intern. Med.*, 82, 534.
 Van Slyke, D. D., and Neill, J. M. (1924). *J. biol. Chem.*, 61, 523.
 Westlake, E. K. (1953). "Disordered Respiratory Function and Carbon Dioxide Narcosis in Emphysema." M.D. Thesis, Cambridge.
 — and Kaye, M. (1954). *British Medical Journal*, 1, 302.
 Yu, P. N. G., Lovejoy, F. W., Joos, H. A., Nye, R. E., and McCann, W. S. (1953). *J. clin. Invest.*, 32, 130.

In 1950 Dr. ERIK WALLER, of Stockholm, presented his library to the University of Upsala (see *Journal*, December 23, 1950, p. 1452). This library comprises about 21,000 items, principally concerned with the history of medicine and science. More than twice the size of Osler's library at McGill, it is one of the most valuable collections of its kind in the world, and represents the result of scholarly collection over a period of forty years. It includes 150 books printed before 1500, a hundred editions of Vesalius (including a unique copy of an edition of the *Epitome*), fifty editions of Harvey, forty-three of Paré, and a large collection of Linneana. Almost all the great names in medicine are represented; there are also many works on the history of medicine. The catalogue of the Bibliotheca Walleriana has now been compiled (in English) by the university librarian of Upsala and is to be published early next year by Messrs. Almqvist and Wiksell, Stockholm, at a subscription price of 175 Swedish kronor (200 kr. after December 31).

THE FACTOR OF INFECTION IN HEART FAILURE

BY

F. J. FLINT, M.A., D.M., M.R.C.P.

Physician to the City General Hospital, Fir Vale Infirmary,
and Nether Edge Hospital, Sheffield

"A neglected cold is frequently the original cause
of the most severe diseases of the heart."—

LAENNEC, 1834.

This review of 300 patients suffering from congestive heart failure (159 males and 141 females) who were admitted consecutively to the City General Hospital, Sheffield, between March 17, 1952, and March 16, 1953, is designed to call attention to the high incidence of respiratory infections in heart failure and to demonstrate their importance as the commonest precipitating cause of heart failure, even in patients with intrinsic heart disease.

In this survey a diagnosis of congestive heart failure demanded an unequivocal rise of cervical venous pressure above the sternal angle during all phases of respiration, and either peripheral oedema or hepatic engorgement. In most cases all three signs were present.

Each patient was examined by me for the purpose of this investigation and a full clinical history was recorded on a standard "pro-forma" which paid particular attention to respiratory symptoms. Routine investigation comprised an electrocardiogram, an x-ray film and screening of the chest, leucocyte count, examination of the urine and sputum, and estimation of the haemoglobin and Wassermann and Kahn reactions.

Clinical Material

Cases having more than one cause are classified under the heading of the major lesion, except for 12 cases of cor pulmonale in which the pulmonary lesion was thought to be predominant, but which are classified under the heading of the associated cardiac lesion and designated "associated cor pulmonale."

1. *Cor Pulmonale*.—Total, 76 (64 males, 12 females); 26 deaths; 24 necropsies. All these patients had severe lung disease, manifested central cyanosis, and had sinus rhythm. None showed evidence of hypertensive, ischaemic, rheumatic, or other intrinsic heart disease.

Chronic bronchitis	..	..	..	..	42 cases
Bronchiectasis	..	..	..	..	21 "
Asthma	..	..	..	..	5 "
Pneumoconiosis	..	..	..	..	5 "
Severe kyphoscoliosis	..	..	..	..	2 "
Organizing pneumonia	..	..	..	..	1 case

2. *Rheumatic and Non-specific Valvular Lesions*.—Total 68 (26 males, 42 females); 18 deaths; 14 necropsies.

Isolated mitral valve disease	..	..	..	..	38 cases
Isolated aortic valve disease	..	..	..	..	9 "
Combined aortic and mitral valve disease	..	..	..	..	21 "
Associated cor pulmonale	..	..	..	..	3 "

3. *Ischaemic Heart Disease*.—Total, 65 (33 males, 32 females); 34 deaths, 23 necropsies.

Recent myocardial infarction	..	..	..	..	26 cases
Old myocardial infarction	..	..	..	..	28 "
Infarction not proved (angina in all)	..	..	..	..	11 "
Associated hypertensive heart disease	..	..	..	..	7 "
Associated aortic stenosis	..	..	..	..	1 case
Associated cor pulmonale	..	..	..	..	4 cases

4. *Hypertensive Heart Disease*.—Total, 63 (26 males, 37 females); 24 deaths; 20 necropsies.

"Primary hypertension"	..	..	..	..	49 cases
Chronic nephritis with uraemia	..	..	..	..	11 "
Acute nephritis	..	..	..	..	3 "
Associated cor pulmonale	..	..	..	..	4 "

5. *Miscellaneous Group*: (a) *Syphilis*.—Total, 6 (5 males, 1 female); 2 deaths; 2 necropsies.

Aortitis with aortic incompetence (W.R. pos.) 5 cases

Aortic aneurysm 1 case

Associated cor pulmonale 1 „

(b) *Severe Anaemia*.—Total, 9 (2 males, 7 females); no death. (Hb 30%–50%, 2 cases; Hb <30%, 7 cases.)

Pernicious anaemia 6 cases

Iron deficiency anaemia 1 case

Myelomatosis 1 „

Carcinomatosis (breast) 1 „

(c) *Thyrototoxicosis*.—Total, 2 (both females); no death.

(d) *Severe Liver Disease*.—Total, 4 (2 males, 2 females); 3 deaths; 2 necropsies.

Hepatic cirrhosis 2 cases

Metastatic carcinoma 2 „

(e) *Congenital Heart Disease*.—Total, 2 (females); 1 death; 1 necropsy.

Atrial septal defect 1 case

Patent ductus arteriosus 1 „

(f) *Aetiology Uncertain*.—Total, 5 (1 male, 4 females); 3 deaths; 2 necropsies.

Seasonal Incidence of Heart Failure

The seasonal incidence of admissions in this series is described in Figs. 1–5. There were also two cases with pulmonary tuberculosis, which is not listed in the diagrams as a respiratory infection.

Cor pulmonale was less common in the summer, only 17 cases being admitted during the months of May to October, but 59 cases from November to April. In the other groups, with the exception of the miscellaneous cases, the incidence of admissions was about twice as high in the winter as in the summer, suggesting that this was due to the prevalence of respiratory infections during the winter months.

FIG. 1.—Incidence of cor pulmonale. May–October: 17 cases—acute respiratory infections 17; deaths 7. November–April: 59 cases—acute respiratory infections 57; deaths 19.

FIG. 2.—Incidence of ischaemic heart disease. May–October: 22 cases—acute respiratory infections 13; deaths 12. November–April: 43 cases—acute respiratory infections 23; deaths 22.

FIG. 3.—Incidence of hypertensive heart disease. May–October: 23 cases—acute respiratory infections 11; deaths 8. November–April: 40 cases—acute respiratory infections 14; deaths 16.

FIG. 4.—Incidence of rheumatic heart disease. May–October: 24 cases—acute respiratory infections 4; deaths 9. November–April: 44 cases—acute respiratory infections 17; deaths 9.

FIG. 5.—Miscellaneous group: severe anaemia, thyrototoxicosis, syphilis, congenital heart disease, severe liver disease, and others. May–October: 13 cases—acute respiratory infections 2; deaths 0. November–April: 15 cases—acute respiratory infections 7; deaths 9.

Incidence of Respiratory Infections and of Other Precipitating Causes of Heart Failure

Of 300 cases in all groups, 167 showed evidence of bronchitis, pneumonia, or other respiratory infection. In 156 of these cases heart failure was immediately preceded by the infection which was present on admission to hospital and which usually began as a cold or influenza (Table I). In the remaining 11 the respiratory infection was usually of the aspiration type, occurring in patients who were comatose or semicomatose from cerebral vascular thrombotic lesions or uraemia. It is suggested that in the majority

of cases a respiratory infection was not merely a secondary or terminal factor but the immediate cause of heart failure because the first symptoms—coryza, sore throat, or cough with purulent sputum—were attributable to respiratory infection rather than to heart failure. Table I describes the incidence and nature of the primary infections occurring in the different groups, but does not include those infections which were believed to be secondary; it also summarizes the other causes of heart failure.

TABLE I.—*Precipitating Causes of Heart Failure—All Groups:*
159 Males; 141 Females

	Ischaemic Heart Disease	Hypertensive Heart Disease	Rheumatic Heart Disease	Miscellaneous Group	Cor Pulmonale	All Groups Combined
I. Diseases of the heart						
Recent myocardial infarction	25	—	—	—	—	25
Active rheumatic carditis	1	1	1	—	—	3
Bacterial endocarditis	—	—	3	—	—	3
II. Diseases of the lungs						
Acute bronchitis	14	16	14	5	54†	103
Pneumonia:						
All cases	15	7	6	3	20	51
Lobar, segmental	10	4	3	1	2	20
Bronchopneumonia	4	2	2	2	13	23
Lung abscess*	1	1	1	—	3	6
Empyema	—	—	—	—	1	1
Organized pneumonia	—	—	—	—	1	1
Tuberculosis	—	—	2	—	—	2
Pulmonary embolism	2	2	7	—	—	11
III. Factors causing hypervolaemia						
Anaemia:						
Chronic anaemia	—	—	1	9	—	10
Massive haemorrhage from gastric or duodenal ulcer	—	—	4	—	—	4
Sodium and water retention:						
Acute nephritis	—	3	—	—	—	3
Chronic nephritis—uraemia	—	9	—	—	—	9
Prostatic hypertrophy (urinary retention)	1	2	—	—	—	3
Insulin	1	1	—	—	—	2
IV. Cardiac tamponade						
Pericardial effusion	—	—	1	—	—	1
V. Miscellaneous						
Cerebral thrombosis—hemiplegia	—	3	—	—	—	3
Paroxysmal auricular fibrillation	—	1	2	—	—	3
Myxoedema	—	1	—	—	—	1
VI. Precipitating cause not elicited						
	6	17	27	11	2	63
Total No. of Patients	65	63	68	28	76	300

* Five patients with lung abscess also had bronchial carcinoma.

† One patient with bronchitis also had a tension pneumothorax.

Table I shows that respiratory infections precipitated heart failure in 74 of the 76 patients with cor pulmonale: bronchitis in 54, bronchopneumonia in 13, lobar or segmental pneumonia in 2, lung abscess or empyema in 4, and an unusual form of diffuse organizing pneumonia in the other. Bronchial infections in this group were thus predominant, and cultivation of the sputum yielded a mixed growth of organisms: of 42 cases whose sputum was thoroughly examined, including mouse inoculation, pneumococci were isolated from 30 and *Haemophilus influenzae* from 10.

In the 224 cases of heart failure not due to cor pulmonale, respiratory infections precipitated heart failure in 82: bronchitis in 49, lobar pneumonia in 18, bronchopneumonia in 10, and lung abscess in 3. Two patients had pulmonary tuberculosis, in one as a pleural effusion, in the other as a spreading parenchymal lesion. The signs of pneumonic consolidation were often masked by the heart failure. Pyrexia was often absent because of peripheral circulatory failure. In many cases bronchitis was detected only if care was taken to inspect the sputum. Unilateral chest dullness was more often due either to a pneumonia or to an effusion secondary to pulmonary infarction than to a simple hydrothorax. Tubular breathing was sometimes absent, probably because of bronchial occlusion by pus or oedema fluid.

There were 144 patients in whom there was no evidence that heart failure had been precipitated by bronchitis or pneumonia. Precipitating causes of the heart failure, which are summarized in Table I, were elicited in 81 of these, and in many of the remaining 63 cases it was thought that heart failure had been precipitated by a cold or influenza.

Considering the 156 patients with precipitating respiratory infections, 11 of the 18 who were over 70 years of age died, compared with 42 of the remaining 138 (Table II). Respiratory infections were thus particularly lethal in patients

TABLE II.—*The Age Distribution and Mortality Rate of Patients Whose Heart Failure was Precipitated by Bronchitis or Pneumonia*

Aetiology	Cases under 70		Cases over 70	
	All Cases	Deaths	All Cases	Deaths
Ischaemic heart disease	18	4	11	8
Hypertensive heart disease	19	5	4	2
Rheumatic heart disease	22	6	—	—
Miscellaneous group	8	4	—	—
Cor pulmonale	71	23	3	1
All groups	138	42	18	11

over 70, especially those with ischaemic heart disease, but the high recovery rate in those under 70 demonstrates that these infections are by no means to be regarded as terminal events.

Causes of Death

Heart failure disturbs the functioning of all organs of the body, so it is often difficult to assess the precise cause of death. In many cases, however, the objective signs of congestive failure such as peripheral oedema, pulmonary oedema, and raised venous pressure have disappeared before death, which may be due to some complicating factor.

117 patients died—111 during their first admission to hospital and 6 during a subsequent admission. Table III

TABLE III.—*The Causes of Death Elicited at Necropsy in Cases of Heart Failure: 88 Cases*

	Ischaemic Heart Disease	Hypertensive Heart Disease	Rheumatic Heart Disease	Miscellaneous Group	Cor Pulmonale	All Groups
No. of cases: Total	65	63	68	28	76	300
Deaths during first admission	34	24	18	9	26	111
No. of cases: Deaths during subsequent admission	3	—	2	—	1	6
No. of cases: Necropsies	23	20	14	7	24	88
Causes of death						
I. Respiratory infections: Total	7	5	2	2	22	38
Pneumonia:						
All cases	6	4	1	1	9	21
Lobar, segmental	3	2*	—	—	—	5
Bronchopneumonia	2	2	1	1	7	13
Abscess	1	—	—	—	—	1
Empyema	—	—	—	—	1	1
Organized pneumonia	—	—	—	—	1	1
Acute bronchitis with respiratory insufficiency	1†	1†	1†	1	13	17
II. Other causes:						
Cardiac failure with pulmonary oedema	9	2	5	1	—	17
Rupture of the heart	2	—	—	—	—	2
Obstruction of mitral valve by left auricular thrombus	—	—	2	—	—	2
Tension pneumothorax	—	—	—	1	—	1
Pulmonary embolism	3	2	3	—	—	8
Uraemia	—	9	—	—	—	9
Massive gastro-intestinal haemorrhage	2	—	—	—	2	4
Cerebral: haemorrhage, embolism, thrombosis	—	2	1	—	—	3
Bacterial endocarditis	—	—	1‡	—	—	1
Liver failure	—	—	—	1	—	1
Carcinomatosis	—	—	—	1	—	1
Uncertain	—	—	—	1	—	1

* One of these two patients also had intestinal obstruction, the other diabetic ketosis.

† Pneumoconiosis.

‡ This patient died from acute pancreatitis due to bacterial embolism.

gives the principal cause of death in 88 of the 117 patients on whom post-mortem examination was permitted. Permission for examination was granted in only 11 of the 23 patients over 70. Death occurred within 48 hours of admission to hospital in only 23, nine of whom had coronary thrombosis.

Uncomplicated heart failure was the cause of death in only 17 of the 88 cases. In 21 cases death was due to pneumonia which had precipitated heart failure. Pneumonia of the secondary or hypostatic type occurred only if the patient had been in coma or semicomatose; it was revealed in several patients who had been unconscious because of a cerebral vascular accident or uraemia.

There is good reason to believe that in nearly all cases of *cor pulmonale*, and in at least 16 of the 64 cases in other groups, death was directly attributable to a respiratory infection which itself had been the immediate cause of heart failure.

Discussion

It has long been accepted that congestive cardiac failure in cases of *cor pulmonale* is precipitated by a respiratory infection. In persons with grossly diminished functioning lung tissue the asphyxiating process induced by respiratory infections is thought to give rise to pulmonary hypertension, sodium and water retention, and, subsequently, failure of the right heart (Harvey *et al.*, 1951; Mounsey *et al.*, 1952; Donald, 1953). In patients with congestive heart failure due to ischaemic heart disease, hypertensive heart disease, rheumatism and other causes, however, hypoxia and hypercapnia are only slight in degree compared with the gaseous disturbance in *cor pulmonale* (Platts, 1953), so that another explanation must be sought for the mechanism whereby in those other forms of heart disease congestive heart failure is often precipitated by a respiratory infection.

There are at least two possible explanations. First, in the case of patients suffering from either left heart failure or mitral stenosis, the resulting pulmonary congestion causes pulmonary oedema, which is an excellent medium for the growth of bacteria even of low virulence. Thus patients with commencing pulmonary congestion are particularly susceptible to bronchitis or pneumonia during the course of a cold or influenza; and this infection, by potentiating the development of oedema fluid, may increase the pulmonary resistance to right ventricular output and lead to overloading.

The second possibility is that the infection may, directly or indirectly, damage the myocardium. There is no doubt that, in common with other infections, pneumonia can cause myocarditis, which, especially in persons with pre-existing heart disease, may lead to cardiac failure. Saphir (1941, 1942), in analysing the cause of myocarditis in 240 cases at necropsy, considered that 19 were accounted for by bronchopneumonia and 7 by lobar pneumonia. Saphir and Amromin (1948), in a study of the hearts at post-mortem examination of 67 patients who had died of pneumonia, found histological evidence of myocarditis in 26 (38.8%), in that the heart muscle was flabby, the ventricles were dilated, the myocardium contained haemorrhages and in some presented a tigroid appearance, and there were petechial haemorrhages in the pericardium. Histologically, in every instance there were inflammatory cells with exudate in the interstitial tissues, and scattered areas of degeneration of muscle fibres. These changes were scattered throughout the heart and would sometimes have been missed if serial sections had not been taken.

Electrocardiograms taken during and immediately after severe pneumonia may show various arrhythmias, low voltage, and sometimes important changes such as all grades of heart block and inversion of the T wave in standard lead I or in the left ventricular chest leads (Wood, 1950). Thomson *et al.* (1946) observed flattening or depression of the T wave in 35 (43%) of 82 cases of pneumonia, which in 23 cases was reversible. It is likely that in patients with pre-existing

coronary artery disease the T-wave changes, which are similar to those described by Wood and his colleagues (1950) as occurring on exercise, are induced by acute coronary insufficiency.

The most marked circulatory disturbance in pneumonia and other severe infections is peripheral circulatory failure due either to paralysis of the nerve centres or to paralysis of the smaller arterioles and capillaries. The state of shock resulting in a fall of blood pressure may further embarrass the circulation by reducing the coronary blood supply.

Myocarditis in pneumonia is unlikely to be a common cause of congestive heart failure. More frequent perhaps than is usually supposed, it is, however, most likely to occur in the fulminant form of pneumonia before there has been time for congestive heart failure to develop. Bronchitis, which is rarely associated with bacteraemia, is unlikely to produce myocarditis. The relatively high incidence of bronchitis as an accompaniment of heart failure in patients with non-pulmonary heart disease (49 of 244 cases in the present series) suggests that respiratory infections embarrass the circulation by some mechanism which has not yet been elucidated.

Conclusion

The present series illustrates both the necessity and the difficulty of arriving at a complete diagnosis, which should include the precipitating cause of failure as well as the basic cardiac lesion. Analysis of the present series (Table I) clearly shows how diverse and complex are these factors. Bronchitis and pneumonia were together responsible for failure in half the cases and for death in two-fifths. Owing to the prevalence of respiratory infections in industrial areas, it is unlikely, however, that the figures are applicable to the country as a whole.

The clinical manifestations of respiratory infections tend to be masked by heart failure, and the possibility of infection must be continuously borne in mind. In a patient with heart disease, bronchitis is likely to be serious; therefore, examination is not complete without inspection of the sputum.

In many cases of heart failure, particularly those occurring in the winter, chemotherapy is probably more important than any other single item of treatment, more important even than digitalis or mersalyl. Further work is in progress to discover which antibiotic is the most useful for the treatment of bronchitis, but for most forms of pneumonia the drug of choice initially is penicillin (M.R.C. Report, 1951; Flint, 1953).

Summary

From a study of 300 cases of heart failure in an industrial city, it was found that over half (167 cases) had some form of respiratory infection. In 156 cases there was good evidence that the respiratory infection was the precipitating cause of failure (bronchitis in 103, pneumonia in 51, tuberculosis in 2), and in only 11 patients, most of whom were comatose, was it thought to be secondary.

Heart failure was precipitated by a respiratory infection in 74 of the 76 patients with *cor pulmonale* and in 82 of the remaining 224 patients with other forms of heart disease. The incidence of heart failure in winter was twice that in summer.

Post-mortem examination was performed in 88 cases. Death was due to pneumonia in 21 cases and to acute bronchitis in a further 17.

The mechanism whereby acute respiratory infections give rise to heart failure is discussed.

It is suggested that antibiotics are at least as important as either digitalis or mersalyl in the treatment of heart failure.

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REFERENCES

- Donald, K. W. (1953). *British Medical Journal*, **1**, 415, 473.
 Flint, F. J. (1953). D.M. Thesis. Oxford University.
 Harvey, R. M., Ferrer, M. I., Richards, D. W., and Cournand, A. (1951). *Amer. J. Med.*, **10**, 719.
 Laennec, R. T. H. (1834). *A Treatise on the Diseases of the Chest and on Mediate Auscultation*, translated by J. Forbes, 4th ed. London.
 Medical Research Council (1951). *British Medical Journal*, **2**, 1361.
 Mounsey, J. P. D., Ritzmann, L. W., Selverstone, N. J., Briscoe, W. A., and McLemore, G. A. (1952). *Brit. Heart J.*, **14**, 153.
 Platts, M. M. (1953). *Clin. Sci.*, **12**, 63.
 Saphir, O. (1941). *Arch. Path., Chicago*, **32**, 1000.
 — (1942). *Ibid.*, **33**, 88.
 — and Amromin, G. D. (1948). *Ann. intern. Med.*, **28**, 963.
 Thomson, K. J., Rutstein, D. D., Tolnach, D. M., and Walker, W. H. (1946). *Amer. Heart J.*, **31**, 565.
 Wood, P. (1950). *Diseases of the Heart and Circulation*. Eyre and Spottiswoode, London.
 — McGregor, M., Magidson, O., and Whittaker, W. (1950). *Brit. Heart J.*, **12**, 363.

INSULIN RESISTANCE

BY

DOUGLAS HUBBLE, M.D., F.R.C.P.

Physician, Derbyshire Royal Infirmary, Derby City Hospital,
and Derbyshire Hospital for Sick Children

Insulin resistance in diabetics is usually defined as a state in which more than 200 units of insulin daily are required to lower the blood sugar to normal levels, such resistance being maintained for not less than 48 hours. This definition, although arbitrary, may be usefully retained until the nature of insulin resistance is understood. It is well recognized that infection and ketosis increase insulin requirements and that insulin resistance is present in some patients in diabetic coma, though whether the involved mechanisms are related to the insulin resistance which occurs in the absence of these states is quite unknown.

It is also recognized that the young insulin-sensitive diabetic oscillates rapidly from hypoglycaemia to hyperglycaemia and ketosis, even under controlled conditions in hospital, and in the absence of infection or other relevant environmental disturbance. In such children there is also a notable disposition to nocturnal hyperglycaemia. Payne (1953) has found that this instability of insulin control is not uncommon in diabetic girls at puberty, and that it can sometimes be avoided by a small dose of oestrogen given in the premenstrual phase.

Smelo in 1948 reviewed 54 cases of insulin resistance in the English literature to that time. Only two of these cases occurred in children. For the entire series of 54 cases, Smelo records a death rate of 41%. He regards the prognosis of the condition as relatively benign, however, and suggests that more careful control and the use of larger doses of insulin would achieve more successful results.

Joslin *et al.* (1952) listed a further 20 cases from the New England Deaconess Hospital, and two of these were in children. The first a boy of 12 years, whose resistance lasted for 8–10 days and required a maximum of 210 units daily; the second a girl of 14 years, whose resistance lasted more than one year and whose maximum requirement of insulin was 470 units daily. The boy's resistance was associated with an allergic sensitivity to all insulins except the crystalline variety, and the girl's resistance was associated with abscesses on the thigh.

Although children are commonly classified as insulin-sensitive, it is by no means uncommon for them to require more insulin for stabilization of their blood sugar than would be regarded as their expected pancreatic secretion. Although this insulin resistance is commonly taken to be due to the action of contra-insulin hormones, as in diabetic girls at puberty, there is no objective evidence for this. In fact, the only exact hint regarding the possible mechanisms involved in insulin resistance derives from Bornstein's work (1953). He injected into insulin-resistant patients 300 units of crystalline insulin intravenously, and by his method of insulin assay was unable in one hour to demonstrate any insulin in the plasma.

There is now to be related the unhappy history of a diabetic girl whose insulin resistance was of a degree hitherto unrecorded, and in whom the resistance was phasic. The resistant phases appeared to be premenstrual and the phases of insulin sensitivity appeared to succeed the menstrual flow.

An Extreme Case of Insulin Resistance

A.B., aged 13 years, a grammar-school girl, was admitted to the children's ward of the Derby City Hospital on December 10, 1951, suffering from diabetic ketosis. The symptoms of diabetes had been present for two months. She recovered without the use of intravenous saline and was discharged from hospital on December 23—requiring 24 units of soluble insulin twice daily. Her maternal grandmother was said to suffer from diabetes. Her height at this time was 5 ft. 4½ in. (164 cm.), which was four inches (10 cm.) above the average height for a girl of her age. The secondary sex characters were just appearing, but menstrual function was not established.

She attended the children's diabetic clinic at the Derbyshire Hospital for Sick Children during the following year and made excellent progress. Her insulin needs were increased to 60 units of soluble insulin daily in two injections. She was readmitted to the Derby City Hospital on January 9, 1952 (thirteen months after her original admission), for restabilization on a mixture of soluble and zinc protamine insulin. Her height had increased in 1952 by ¾ in. (1.9 cm.) to 5 ft. 5½ in. (166 cm.) and her weight was 8 st. 9 lb. (54.9 kg.). The secondary sexual characters were now fully developed, but the menses had not occurred. Early-morning hypoglycaemia developed with a dose of zinc protamine insulin as small as 8 units, so a mixture of globin insulin 24 units and soluble insulin 28 units was used for a time. In six weeks in hospital she had gained 8 lb. (3.6 kg.) in weight, so her daily ration of carbohydrate (which had previously been "free" except for the restriction of jams, sugar, and sweets) was reduced to 250 g.

On February 26, 1953, while still in hospital, persistent hyperglycaemia developed and she was treated by injections of soluble insulin three- to four-hourly. Despite a steady increase of dosage during the next three weeks, to the amount of 12,160 units by March 20, her blood sugar was seldom below 250 mg. per 100 ml. in the daytime, nor did sugar disappear entirely from the urine. There was intermittent