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A HOSPITAL STUDY OF CONGESTIVE HEART FAILURE, WITH SPECIAL REFERENCE TO COR PULMONALE

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Pulmonary heart failure, or cor pulmonale, is common in some parts of Britain, and Flint (1954) found that it accounted for a quarter of the cases of heart failure admitted to one Sheffield hospital (the City General Hospital). Yet, as was pointed out by Wood (1956), there are few comparative figures, and in the mortality statistics quoted by Southwood (1959) it receives scant mention. During 1954 to 1956 a study was made in hospitals of the Sheffield Hospital Region in order to compare the relative frequency of the various causes of heart failure in Sheffield and in other areas. A secondary purpose of the study was to compare the symptoms and signs, personal habits, occupation, and residence in the patients suffering from various forms of heart failure.

Method of Study

The hospitals chosen for the study were the City General Hospital in Sheffield and the general hospitals in Leicester, Nottingham, Derby, Scunthorpe, Mansfield, and Grimsby. In each hospital all patients with a diagnosis of congestive heart failure were examined as soon as possible after admission and admitted to the study, provided that they showed a raised jugular venous pressure and/or hepatomegaly and also oedema of the lower extremities and/or back. Patients aged 70 or over were excluded because of the difficulty of obtaining histories and personal data from them and because geriatric units were not included in the investigation. It was realized that the study would not provide evidence concerning the total prevalence of heart failure in any town or district, but this disadvantage was inevitable. A record card containing details of the patient (Fig. 1) was completed by a registrar or senior registrar as soon as possible after admission, but in each hospital the case was discussed with a consultant, who was responsible for the ultimate diagnosis and classification. Necropsies were performed whenever possible on those who died, and the records of the findings were completed on a standard form.

*The following participated in this study:— Sheffield (City General Hospital): Drs. F. J. Flint, J. P. Caley, and R. W. Meikle. Derby: Drs. E. J. S. Woolley and D. S. Harling. Leicester: Drs. S. E. Tanner, D. F. Lawson, and H. J. Goldsmith. Nottingham: Drs. W. S. Whimster, J. M. Macfie, and W. R. O. Gosling. Grimsby: Drs. M. Steel and D. I. Gantzer. Mansfield: Drs. J. C. Pease and J. N. Wattie. Scunthorpe: Drs. J. H. D. Millar and V. Kritzing.

The group gratefully acknowledge the assistance of the many physicians who permitted study of their patients and of the pathologists in each hospital who provided special post-mortem reports.

The cost of printing the record cards and expenses incurred during analysis of the records were borne by the Sheffield Regional Hospital Board.

The necropsy findings were taken into account in the final diagnostic classification, and batches of case records, together with x-ray films and electrocardiograms, were reviewed by the consultant in charge of the study in each area with one of the Sheffield workers.

This procedure was followed in order to standardize so far as possible the records of many different observers. Exact diagnostic criteria were not established at the outset, for the objective was that of assigning each case of congestive heart failure to one of a series of diagnostic groups based upon reasonable evidence of the causation of the heart failure. Thus the presence of valvular heart disease with a history either of rheumatic disease or characteristic valvular involvement led to the classification of the patient in the rheumatic group. Patients with hypertension were classified separately from those with evidence of ischaemic heart disease with or without myocardial infarction. As, however, there were many instances of hypertension with ischaemia, all patients with one or both of these conditions were later combined into a single degenerative group. When hypertension existed but the clinical picture was otherwise concordant with cor pulmonale, the patient was classified as a case of cor pulmonale. This was done whether or not the blood pressure returned to normal levels when the heart failure had subsided.

Cor pulmonale was diagnosed in patients with a history and signs of chronic chest disease provided that the clinical, radiological, and electrocardiographic findings were consistent with this diagnosis rather than with ischaemic heart disease. When the cause of heart failure was thought to be thyroid disease, or anaemia, or an acute infection of the lung without preceding chronic disease the case was placed in a "miscellaneous" category. Patients with congenital heart disease, pulmonary embolism leading to acute right heart failure, carcinoma, gross obesity, or without any discoverable cause for the failure were also placed in the miscellaneous group, largely because of the small numbers concerned.

Thus the final classification of each patient depended upon the clinical diagnosis supported by radiological and electrocardiographic evidence and, when available, by the necropsy findings. After conclusion of the assembly of the series, each record card was coded and the data were transferred to a punch-card. The latter cards were sorted in a Powers-Samas machine. The following analysis covers the complete series of patients from Sheffield and Derby, but only those studied during the first winter season in the other areas.

Classification of Chief Diagnostic Groups of Cases of Heart Failure

Table I shows the entire series of 487 cases, divided into the four diagnostic groups of cor pulmonale, degenerative, rheumatic, and miscellaneous cases listed by area. There were 235 patients from the Sheffield

City General Hospital, of whom 96 (41%) were classified as cases of cor pulmonale, and 252 patients from elsewhere of whom 76 (30%) were cases of cor pulmonale. The total number of cases of cor pulmonale was thus 172 of 487 cases (35%). This should be compared with the totals of 165 degenerative cases

COR PULMONALE INVESTIGATION : CASE REPORT		SIGNS ON ADMISSION (contd.)		SIGNS ON ADMISSION (contd.)	
HOSPITAL PHYSICIAN IN CHARGE PATIENT'S OWN DOCTOR PATIENT'S NAME DOCTOR'S ADDRESS SEX AGE HOSPITAL RECORD No. RESIDENCE : Number of years in town Give type of area Number of years in country Give type of area (If residence varied give main type of area, e.g. industrial, country town, colliery village, etc.) OCCUPATIONS : INDUSTRY OR UNDERTAKING : Most recent No. of years Previous No. of years No. of years No. of years No. of years If the answer is "No" or "None" please cross out the appropriate word. If the answer is "Yes" please tick. Insert figures where appropriate.		FUNDI : Normal Haemorrhages Exudate Papilloedema THYROID : Normal Enlarged Nodular FINGER TWITCHING : Absent Present Tremor PULSE : Rate per minute Rhythm : Regular Extrasystoles Fibrillation apex rate/min. Volume : Normal Poor Full Collapsing Paradoxus Alternans Blood Pressure : Systolic Diastolic HEART : Apex beat : Impalpable Present, space IV Present, space V Present, space VI Under 3" from midline 3"-4" from midline Over 4" from midline Apical impulse : Absent Diffuse L.V. thrust R.V. thrust Murmurs : Absent Mitral diastolic Aortic diastolic Aortic stenosis Pulmonary stenosis Basal to-and-fro Pericardial rub Other murmurs (specify) Gallop rhythm : Absent Apical Sternal LUNGS : Normal Emphysema General bronchospasm Basal rales General rales Consolidation Clinical effusion R. side " " L. side " " both sides LIVER : Not palpable Palpable, no. of fingers Pulsating OEDEMA : Absent Ankles and/or sacrum Legs Thighs Flanks Ascites URINE : Specific gravity normal " " low " " high Albumin : Absent Moderate Heavy Casts : Absent Present Cells : R.B.C.s W.B.C.s		BLOOD UREA : Amount in mg. per 100 ml. HAEMOGLOBIN : Percentage HAEMATOCRIT : Percentage WASSERMANN REACTION : Negative Positive ALKALI RESERVE : Volumes per cent ANY OTHER RELEVANT SIGNS : PLEASE SUMMARISE REPORTS ON : ELECTROCARDIOGRAM : X-RAYS : SIGNS AFTER RECOVERY : BLOOD PRESSURE : Systolic Diastolic OEDEMA : Absent If present, specify : JUGULAR VENOUS FILLING : Absent If present, specify : LIVER : Impalpable If palpable, give no. of fingers Pulsating TREATMENT : Restricted fluids Restricted salt Antibiotics (specify) Drugs (specify) Other (specify) CLINICAL DIAGNOSIS : P.M. DIAGNOSIS :	
SMOKING HABITS (now if smoking : before cessation if given up) Most recent amount smoked : No. of cigarettes per day (average) Pipe tobacco, ounces per week Never smoked or odd ones only Total number of years' smoking I stopped, no. of years since smoking Type of smoking : Cigarettes only (pipe < 1 year regly.) Pipe only (cigarettes < 1 year regly.) Mixed cigarettes and pipe smoking PAST HISTORY : Give year of onset or attack(s). Chest disease : Asthma Bronchiectasis Occasional Bronchitis Annual " Habitual " Pneumonia Pulmonary Tuberculosis Silicosis Scoliosis Bronchial Carcinoma Chest operations Rheumatic heart disease : Chorea Arthritis Valvular Angina pectoris : Of effort At rest Other conditions (specify) : Syphilitic Thyroid Renal Congenital Other Previous attacks of congestive failure (number) PAST SYMPTOMS : Give year of onset if known. Dyspnoea (on effort) " (nocturnal) Pain in chest Sputum Haemoptysis Oedema of ankles : Intermittent Persistent Cough : Intermittent Every winter Habitual Wheezing : With bronchitis Habitual		PRESENT ILLNESS : Date of onset Date of admission to hospital Date of discharge/death SYMPTOMS ON ADMISSION DYSPNOEA : Absent Present on exertion (hills) Present on climbing stairs Present at rest Nocturnal attacks COUGH : Absent Present PAIN IN CHEST : Absent Present, pleural Present, anginal Other SPUTUM : Absent Present, mucoid Present, white, frothy Present, mucopurulent Present, purulent Present, bloodstained OTHER SYMPTOMS : (Specify) SIGNS ON ADMISSION MENTAL STATE : Alert Drowsy Disorientated CYANOSIS : Absent Finger nails Ears Lips Tongue FINGER CLUBBING : Absent Moderate Gross HANDS : (assess when patient is warm) Cold Warm Hot FOREARM VEINS : (assess when patient is warm) Normal Constricted Full JUGULAR VENOUS FILLING : (inspir'n and expir'n) Not visible Halfway up neck To angle of jaw (assess with patient at 45° or give angle) EYES : Normal Proptosis Exophthalmos Conjunct'l. chemosis			

FIG. 1

TABLE I.—*Diagnostic Classification of Heart Failure*

Hospital Area	Total No. Cases	Diagnostic Groups of Cases of Heart Failure							
		Cor Pulmonale		Degen-erative		Rheum-atic		Miscel-laneous	
		No.	%	No.	%	No.	%	No.	%
Sheffield City General ..	235	96	41	76	32	46	20	17	7
Derby ..	85	23	27	26	31	24	28	12	14
Leicester ..	75	20	27	26	35	21	28	8	11
Nottingham ..	54	26	48	16	30	7	13	5	10
Others (Grimsby, Mansfield, Scunthorpe)	38	7	18	21	55	8	21	2	5
Total other than Sheffield ..	252	76	30	89	35	60	24	27	11
Grand total ..	487	172	35	165	34	106	22	44	9

(34%) and of 106 rheumatic cases (22%). It appears that the proportion of patients with cor pulmonale was higher in Sheffield and Nottingham than elsewhere, and was lowest in the smaller regional towns, such as Grimsby, Mansfield, and Scunthorpe.

Table II shows the distribution of the patients by age and sex irrespective of the area from which they were drawn. An excess of male patients in both the cor

TABLE II.—*Age and Sex Distribution*

Ages	Sex	Cor Pulmonale		Degen-erative		Rheum-atic		Miscel-laneous		Total No.
		No.	%	No.	%	No.	%	No.	%	
		No.	%	No.	%	No.	%	No.	%	
15-24 {	M	—	—	1	1	—	—	—	—	1
	F	—	—	—	—	1	1	—	—	1
25-34 {	M	2	1	3	3	7	19	1	2	13
	F	—	—	2	3	5	7	2	6	9
35-44 {	M	11	8	2	2	14	38	1	9	28
	F	7	18	1	2	15	22	3	9	26
45-54 {	M	42	32	19	19	3	8	2	25	66
	F	13	34	16	25	24	35	8	25	61
55-64 {	M	59	44	42	41	8	22	7	44	116
	F	13	34	28	45	21	31	14	44	76
65-69 {	M	20	15	35	34	5	14	1	16	61
	F	5	13	16	25	3	4	5	16	29
Total {	M	134	100	102	100	37	100	12	100	285
	F	38	100	63	100	69	100	32	100	202
Ratio ..	M/F	3.5:1		1.6:1		1:1.8		1:2.6		1.4:1

pulmonale and degenerative groups contrasts with the excess of female patients in the rheumatic and miscellaneous groups. The ratio of 3.5 males to 1 female in cor pulmonale is lower than that of 5.4 to 1 found in the series of Sheffield patients with cor pulmonale reported by Stuart-Harris and Hanley (1957). The largest number of cases fell between the ages of 45 and 64, and the proportions by age did not differ greatly in the various diagnostic groups. It must not be forgotten that the study did not include patients aged 70 or over.

Table III records the total number and proportion of deaths and of necropsies. The overall death rate was high (35%), but was similar in the various groups. Among the 165 patients with degenerative heart disease there were 49 fatalities, 26 of which occurred in the 83 patients with hypertension only, and 19 more in patients with or without evidence of hypertension who had suffered recent myocardial infarction. Thus the death rate in patients with recent infarction was 46%, which was the highest in the series. The proportion of fatal cases on which necropsies were performed was much the same in the various groups, and was 73% of the total.

Table IV shows the underlying chest diseases and associated conditions found in the 172 cases of cor pulmonale, 96 of whom were from Sheffield and 76

TABLE IV.—*Associated Conditions in 172 Cases of Chronic Cor Pulmonale*

	96 Cases from Sheffield	76 Cases from Other Areas	172 Cases in Total
<i>Chest Disease</i>			
Total bronchitis and/or emphysema ..	92	74	166
Bronchitis and/or emphysema alone ..	64	38	102
Bronchiectasis ..	14 (3)	16 (2)	30 (5)
Kyphoscoliosis ..	9 (1)	3	12 (1)
Asthma ..	4	5	9
Pneumoconiosis and other fibrosis ..	4	3	7
Pulmonary embolism and thrombosis ..	2	4	6
Pulmonary tuberculosis ..	3	3	6
Carcinoma lung ..	2*	1	3
Bronchopneumonia ..	3	10	13
Lung abscess ..	—	2	2
1 case each of pneumothorax, congenital cystic lung, and Marfan's syndrome			
<i>Other Disease</i>			
Hypertension ..	16	10	26
Anaemia with Hb 70% ..	4	2	6
Ischaemic heart disease ..	4	—	4
Recent myocardial infarct ..	—	1	1
Rheumatic heart disease ..	—	2	2
1 case each of nephrosis, cystic kidney, renal calculus, chronic alcoholism, and acute glaucoma.			

* One case possibly gastric in origin.

Figures in parentheses where the condition was the sole diagnosis.

from other areas. Bronchitis and/or emphysema was present in 92 of the Sheffield patients (96%) and in 74 of the others (98%), and was the only chest disease mentioned in 64 Sheffield and 38 other patients. Bronchiectasis was present in 30 patients, and was the sole diagnosis in three Sheffield cases and two other cases. Kyphoscoliosis was noted in 12 patients, and was the sole diagnosis in one Sheffield case. Other forms of chest disease such as asthma, pneumoconiosis, pulmonary tuberculosis, pulmonary embolism or thrombosis, carcinoma, pneumonia, lung abscess, pulmonary oedema, and pneumothorax were found in small numbers of patients who also had chronic bronchitis and/or emphysema. The proportion of

TABLE III.—*Deaths and Post-mortem Examinations*

Hospital Area	Ages	Cor Pulmonale			Degenerative			Rheumatic			Miscellaneous			All		
		No.	Deaths	P.M.	No.	Deaths	P.M.	No.	Deaths	P.M.	No.	Deaths	P.M.	No.	Deaths	P.M.
		No.	Deaths	P.M.	No.	Deaths	P.M.	No.	Deaths	P.M.	No.	Deaths	P.M.	No.	Deaths	P.M.
Sheffield ..	<45	10	2	2	5	2	2	13	5	5	2	—	—	30	9	9
	45+	86	30	23	71	16	14	33	11	9	15	5	4	205	62	50
Other areas ..	<45	10	4	2	4	1	1	29	10	8	5	4	4	48	19	15
	45+	66	31	25	85	30	18	31	10	3	22	9	5	204	80	51
Total ..	<45	20	6	4	9	3	3	42	15	13	7	4	4	78	28	24
	45+	152	61	48	156	46	32	64	21	12	37	14	9	409	142	101
All ages ..		172	67	52	165	49	35	106	36	25	44	18	13	487	170	125
		38%			30%			34%			41%			35%		

patients with various chest diseases is similar to that found in the series of cases of cor pulmonale reported by Stuart-Harris and Hanley (1957). Associated conditions other than hypertension (26 cases) were uncommon (Table IV).

Chief Clinical Findings in Three Groups of Cases of Heart Failure

The clinical details obtained by history and by physical examination at the time of admission were of course used in classifying the patients in one or other of the diagnostic groups. The findings which were of chief differential value in the three principal groups are totalled and set out in Table V, of which section A shows the past history and symptoms on admission. Recurrent attacks of bronchitis were more than three times as common in the cases of cor pulmonale than in either of the other groups. A similar excess existed in those with a past history of asthma or of pneumonia in the cor pulmonale cases. Previous attacks of

congestive failure had occurred in all the various groups of patients. Rheumatic manifestations, including chorea, arthritis, and valvular disease, occurred almost exclusively in the rheumatic cases. A past history of anginal chest pain was obtained in 45 (27%) degenerative, in 11 (6%) cor pulmonale, and in 8 (8%) rheumatic cases.

The symptoms present on admission and listed in Table V are selected because of their differential value, and dyspnoea, which was present in almost all of the patients, is omitted. Cough was present in two-thirds or more of the patients in each group. A mucoid sputum was of no differential value, but a mucopurulent or purulent sputum was more than four times as common in the cases of cor pulmonale. Chest pain other than angina was, however, of little differential value; anginal pain was naturally commoner in the degenerative cases, and was present on admission in 31 cases (19%).

Section B of Table V gives the principal physical signs at the time of admission. The high incidence in cor pulmonale cases of cyanosis of the lips (93%) and of the tongue (83%) is particularly noteworthy. Cyanosis of the lips was present in only half of the patients with degenerative or rheumatic disease, and the tongue was noted to be cyanotic in only one-fifth of these patients. Warm peripheral extremities, chemosis of the conjunctivae, and twitching of the fingers, which are often regarded as of diagnostic value in cor pulmonale, were present in less than one-quarter of these patients, yet were even less common in the other groups. A drowsy or mentally disorientated state was, however, present in 40% of the patients with cor pulmonale and was twice as common in these as in the other groups of patients.

Some findings in regard to the heart and peripheral circulation deserve special comment. 95% or more of the patients had a raised jugular venous pressure on admission, and therefore there were few patients admitted to the series on the basis of hepatomegaly without raised venous pressure in the neck. In the cases of cor pulmonale the cardiac rhythm was usually regular, but auricular fibrillation was present in nine patients. Auricular fibrillation occurred more frequently in the patients with hypertension or ischaemic disease, yet it was found in only 22% compared with 70% of the rheumatic cases. A diastolic blood pressure in excess of 100 mm. Hg was present in half of the cases of degenerative disease, compared with 15% of cor pulmonale and 9% of rheumatic cases. When palpable the cardiac impulse was usually right ventricular in type in cor pulmonale, left ventricular in degenerative cases, and right or left (or both) in rheumatic disease. Murmurs were of course a feature of valvular disease and were uncommon in cor pulmonale, but a gallop rhythm was equally common in degenerative and cor pulmonale cases.

It proved difficult to analyse the electrocardiograms in a statistical form, and, in any case, these were not taken in patients who succumbed soon after admission. No attempt was made to code the findings of right or left ventricular hypertrophy. Of the 408 patients on whom reports were available, 37 were stated to have normal electrocardiograms, and these included some patients from each group. A "P pulmonale" wave and right ventricular strain pattern were the chief abnormalities in cor pulmonale. A left ventricular strain pattern was characteristic of hypertension, and the changes usually interpreted as being due to

TABLE V.—Chief Clinical Findings in Three Main Groups of Cases of Heart Failure

	Cor Pulmonale 172 Cases		Degen- erative 165 Cases		Rheumatic 106 Cases	
	No.	%	No.	%	No.	%
<i>A. Past History and Symptoms on Admission</i>						
Past history:						
Recurrent bronchitis ..	146	85	39	24	22	21
Asthma ..	35	20	11	7	1	1
Bronchiectasis ..	17	10	1	1	—	—
Pneumonia ..	76	44	25	15	27	26
Tuberculosis ..	6	3	4	2	1	1
Silicosis or pneumoconiosis ..	4	2	—	—	—	—
Scoliosis or kyphoscoliosis ..	12	7	2	1	—	—
Previous congestive failure ..	35	20	26	16	41	39
Rheumatic manifestations ..	6	3	12	7	68	64
Anginal pain ..	11	6	45	27	8	8
Symptoms on admission:						
Cough ..	154	90	107	65	74	70
Sputum: mucoid ..	24	14	31	19	32	30
" mucopurulent or						
" purulent ..	98	57	20	12	8	8
Anginal pain ..	9	5	31	19	9	9
Pleural and other chest pain ..	23	13	25	15	20	19
<i>B. Signs on Admission</i>						
General:						
Drowsiness and disorientation ..	71	41	34	21	7	7
Cyanosis of lips ..	159	93	69	42	52	49
" tongue ..	142	83	33	20	18	17
Clubbing of fingers ..	69	40	12	7	14	13
Hands cold ..	11	6	45	27	30	28
" hot ..	35	20	8	5	3	3
Conjunctival chemosis ..	39	23	5	3	1	1
Twitching of fingers ..	28	16	2	1	1	1
Peripheral circulation:						
Raised jugular venous pressure ..	169	98	156	95	100	95
Auricular fibrillation (pulse) ..	9	5	37	22	74	70
Diastolic B.P. 100 mm. Hg or more ..	26	15	83	50	9	9
Cardiac signs:						
Impalpable cardiac impulse ..	74	43	51	31	5	5
Diffuse ..	64	37	47	29	22	21
Right ventricular ..	59	34	5	3	35	33
Left ..	12	7	77	47	57	54
Murmurs ..	17	10	68	41	105	99
Gallop rhythm at apex ..	25	15	49	30	11	10
" " " sternum ..	35	20	17	10	2	2
Electrocardiograms:						
No. done ..	159	100	154	100	95	100
" normal ..	20	13	14	9	3	3
Auricular fibrillation ..	8	5	26	17	70	74
P pulmonale ..	91	57	—	—	3	3
Right ventricular strain ..	64	40	—	—	14	15
Left ..	11	7	69	45	27	29
Chest signs:						
Clinical emphysema ..	147	86	36	22	7	7
" Bronchospasm " ..	108	63	31	19	12	11
X-rays done ..	149	100	144	100	93	100
X-ray suggestive of emphysema ..	72	48	14	10	2	2
" " other chronic						
" lung disease ..	34	23	10	7	2	2

ischaemia were almost confined to the degenerative group.

Physical signs in the chest which suggested emphysema were found in 86% of the patients with cor pulmonale and were also present in 22% of the degenerative cases. Radiographic appearances suggestive of emphysema were present in 48% of those cases of cor pulmonale in whom x-ray films of the chest were available and in 10% of the degenerative cases. Radiological evidence of other chronic lung disease was found in 23% of the cor pulmonale cases and in 7% of the degenerative cases. Clinical evidence of "bronchospasm" was predominantly found among the cases of cor pulmonale, and it was recorded in 63% of these, compared with 19% of degenerative cases and 11% of rheumatic cases.

The Blood

The results of the estimation of the haemoglobin, the haematocrit, the blood urea, and the plasma alkali reserve are shown in Table VI and in Fig. 2. In spite

FIG. 2

of the many different laboratories concerned and the fact that only some of the patients were tested, the results show both similarities and differences between the various groups of cases. The latter are considered in only three groups—cor pulmonale, degenerative, and rheumatic and miscellaneous—and the distribution of the results is shown in percentages.

The variation in the haemoglobin was considerable in each group of cases. The highest number of patients with a haemoglobin of less than 70 occurred in the miscellaneous group, in which were placed cases of anaemia without other evidence of heart disease. Nevertheless each group included some anaemic cases, and these patients had sometimes suffered from gastrointestinal haemorrhage or long-standing nephritis. The distribution of the haematocrit percentages was remarkably similar in the degenerative and combined rheumatic and miscellaneous cases, about half of whom had values which lay between 40 and 50%. The haematocrits of the cor pulmonale cases were often higher, and 57% of results fell between 45 and 55%. 27% of the cor pulmonale cases had haematocrits in excess of 55%, compared with only 9% of the rheumatic and miscellaneous cases and 2% of the degenerative cases. The haematocrit distribution in cor pulmonale was similar to that recorded by Stuart-Harris and Hanley (1957).

The blood urea was often elevated in all forms of heart failure, and normal values of less than 40 mg. per 100 ml. were present in only 41% of cor pulmonale, 32% of degenerative cases, and 39% of rheumatic and miscellaneous cases. There were a few more cases in the degenerative than in the other groups with a blood urea in excess of 90 mg. per 100 ml., probably because of the inclusion of cases with nephritis in this category.

The venous plasma alkali reserve is a poor substitute for the arterial carbon dioxide content or tension. Nevertheless, as Table VI and Fig. 2 show, the distribution of the alkali reserve was much the same in

TABLE VI
Haemoglobin (%)

Group	Total No.	< 60		60-69		70-79		80-89		90-99		100-109		110-119		120 +	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Cor pulmonale	157	3	2	3	2	15	10	30	20	49	31	35	22	17	10	5	3
Degenerative	150	11	7	10	7	25	17	35	23	39	26	18	12	9	6	3	2
Rheumatic and miscellaneous	140	15	11	13	9	17	12	35	25	26	19	22	16	9	6	3	2

Haematocrit (%)

		< 35		< 35-39		40-44		45-49		50-54		55-59		60-64		65 +	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Cor pulmonale	125	2	2	6	5	11	9	34	27	38	30	18	14	12	10	4	3
Degenerative	97	12	12	18	18	26	27	24	25	15	15	2	2	0	0	0	0
Rheumatic and miscellaneous	103	14	14	17	17	28	27	24	22	11	11	7	7	2	2	0	0

Blood Urea (mg. per 100 ml.)

		< 30		< 30-39		40-49		50-59		60-69		70-79		80-89		90 +	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Cor pulmonale	146	28	19	32	22	40	27	17	12	11	8	3	2	1	1	14	10
Degenerative	147	19	13	28	19	33	23	16	11	13	9	9	6	4	3	25	17
Rheumatic and miscellaneous	126	27	21	23	18	33	26	21	17	5	4	2	2	1	1	14	11

Plasma Alkali Reserve (Volumes %)

		< 35		< 35-39		40-49		50-59		60-69		70-79		80-89		90 +	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Cor pulmonale	148	0	0	1	1	6	4	22	15	37	25	55	37	25	17	2	1
Degenerative	124	10	8	3	2	32	26	38	30	28	22	11	9	1	1	1	1
Rheumatic and miscellaneous	119	5	4	7	6	31	26	45	38	22	19	9	8	0	0	0	0

degenerative and combined rheumatic and miscellaneous groups, and differed from that in the cases of cor pulmonale.

In the degenerative and combined rheumatic and miscellaneous groups 78 and 83% respectively of the values for the alkali reserve lay between 40 and 70 volumes %. There were 11 and 8% of values in excess of 70 volumes % in these cases. But in the cor pulmonale cases only 44% of values lay between 40 and 70 volumes % and 55% were in excess of 70 volumes %. The fact that there were so many high values in the cor pulmonale cases is doubtless explained by the state of respiratory acidosis and carbon dioxide retention in this condition, known from the work of many authors (Baldwin *et al.*, 1949; Platts, 1953).

Therefore both a high haematocrit and a raised plasma alkali reserve may be of differential value in the diagnosis of cor pulmonale, particularly when it is not possible to obtain an analysis of the arterial blood oxygen saturation or carbon dioxide tension.

Relative Frequency of Certain Personal Characters

The record form used during this inquiry contained sections on the duration of residence in various areas, on the present and previous occupations, and on smoking habits. Such information required co-operation from the patients, which could not be given by severely ill or dying patients. It has already been shown (Stuart-Harris and Hanley, 1957) in a symptomatic inquiry carried out in Sheffield by Dr. Marjorie Clifton that the symptoms of bronchitis are correlated less well with the present work of a group of men in industry than with previous work which entailed exposure to dust. For this reason much more careful inquiry of past occupations would have been necessary for valid correlations between the type of occupation and variety of heart failure than that of the present study. It was in fact found that a very large number of occupations had been pursued by the 285 men in the present inquiry. The record of past occupations was not always complete, the degree of exertion and exposure to dust in the various jobs were matters of surmise, and detailed analysis and correlations were therefore abandoned.

The question of residence in various areas was considered by first separating those who had lived primarily in an industrial environment. There were relatively few who had lived in other areas, including rural dwellers and those living in county towns or a seaport such as Grimsby. Data on 339 patients from an industrial environment and 119 from rural and other urban areas were available and are shown by diagnostic classification in Table VII. The patients from Sheffield and Nottingham hospitals were largely resident in an industrial area, the ratio of industrial to other dwellers being 8.6:1 and 6.1:1 respectively. Elsewhere the numbers of industrial and of other dwellers bore a closer relation to each other (1.5:1). The relative proportions of patients from industrial and other areas show slight differences according to the clinical group. More of the industrial dwellers suffered from cor pulmonale (39%) than from any other form of heart failure in both Sheffield and other hospitals, whereas in those living in other types of area and mostly resident elsewhere than Sheffield, degenerative heart failure preponderated (36%). However, the differences are too small to establish a correlation between environment and disease. In any future inquiry many more patients living in a purely rural area should be examined in order to establish evidence concerning this matter.

Finally, the smoking habits recorded in 256 men and 191 women are considered in Table VIII. The number of heavy and moderate smokers among the women was only 35, and was too small for a comparison between smoking habits and the incidence of the various forms of heart failure. There were 30 men who had never smoked and 40 who smoked a pipe only or who had given up cigarette smoking. Moderate cigarette smokers (1-15 a day) totalled 113, and 82 men were heavy smokers (more than 15 cigarettes daily). The distribution of patients according to smoking habits shows an excess of heavy cigarette smokers in cases of cor pulmonale. Thus there were 44 heavy smokers among 134 such patients (33%), compared with only 7 heavy smokers among 49 (14%) rheumatic and miscellaneous cases.

A similar proportion of heavy smokers was noted among the cases of degenerative heart disease, and this

TABLE VII

Type of Residential History	Sheffield			Regional Total			Total		
	Indust.	Other	No Record	Indust.	Other	No Record	Indust.	Other	No Record
Cor pulmonale	80	9	7	52	20	4	132 (39%)	29 (24%)	11
Degenerative	68	5	3	46	38	5	114 (34%)	43 (36%)	8
Rheumatic	38	7	1	30	24	6	68 (20%)	31 (26%)	7
Miscellaneous	12	2	3	13	14	—	25 (7%)	16 (14%)	3
Total	198	23	14	141	96	15	339 (100%)	119 (100%)	29
Ratio (indust./other) ..	8.6:1			1.5:1			2.8:1		

TABLE VIII.—Smoking Habits in 285 Male Cases of Heart Failure

	Never Smoked		Pipe Only or Given Up Cigs. > 5 Years		Cigarettes 1-15/Day		Cigarettes Over 15/Day		No Record of Smoking Habits		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Cor pulmonale	12	9	19	14	52	39	44	33	7	5	134	100
Degenerative	11	11	16	16	38	37	31	30	6	6	102	100
Rheumatic and miscellaneous	7	14	5	10	23	47	7	14	7	14	49	100
Total*	30	11	40	14	113	40	82	29	20	7	285	100
All groups of female cases	152	75	4	2	31	15	4	2	11	5	202	100

* When tested by the χ^2 test (with 4 degrees of freedom) the significance of the association between smoking and the clinical classification is such that it could occur once in five times ($p=0.20$) by chance.

was further studied by subdivision according to the presence or absence of ischaemia in the cases of hypertension. Of 40 hypertensive patients 11 were heavy smokers, compared with 20 of 62 patients with ischaemia. Too much reliance cannot be placed on this slight difference, but the total number of 31 heavy smokers (30%) represents an excess compared with the figure for rheumatic and miscellaneous cases. In neither cor pulmonale nor ischaemic disease was the association with smoking statistically significant.

Discussion

The clinical features of chronic anoxic cor pulmonale which are usually accepted as being essential for the diagnosis are, first, the central cyanosis visible in the tongue and warm extremities; secondly, the presence of an acute chest infection superimposed on chronic lung disease; and, thirdly, right ventricular disease with hypertrophy or electrocardiographic strain in the absence of other causes such as pulmonary embolism, or congenital or valvular heart disease. To these many would add evidence from arterial blood examination of unsaturation with oxygen and a high carbon dioxide tension. These features have not usually been sought by simultaneous study of other forms of congestive failure, and the present investigation has achieved this in a statistical way.

The figures already given for the relative frequency of cyanosis of the lips and tongue, of drowsiness or disorientation, of mucopurulent or purulent sputum, of a past history of bronchitis, of physical signs suggestive of emphysema with obstructed breathing and the various cardiac signs show that there is a distinctive clinical picture which can be recognized by many observers working in different hospitals. Moreover, auricular fibrillation, left ventricular disease, and hypertension are usually absent in cor pulmonale except for a small percentage of patients in whom combined disease may exist. When to the clinical features is added the help given by the venous haematocrit and plasma alkali reserve it appears that confirmation of the diagnosis is open to all with reasonable facilities for clinical investigation.

This study has shown the unquestionable numerical importance of cor pulmonale in the main hospital centres of one region. Yet the limitation of a purely hospital study in areas of a generally similar character is obvious. The rural county of Lincolnshire, for instance, supplied few patients to this study largely because patients with heart failure in country districts tend to be treated at home. The overall prevalence of cor pulmonale in hospital was 35%—a figure even higher than that recorded by Flint (1954). The disease was largely found in males and in those suffering from chronic bronchitis and emphysema. Its frequency may be due to the large size of the problem of this form of chest disease in the areas concerned. If this study had been designed as an epidemiological investigation regions of a more diverse character and with other forms of chest disease, such as tuberculosis or pneumoconiosis, would have been interesting to study. The data concerning the patients' residence are indicative of a general relation between cor pulmonale and life in an industrial environment, as has previously been shown for chronic bronchitis (Stuart-Harris and Hanley, 1957). That rural populations might provide contrasts is obvious. Yet in Belgrade, Slavković *et al.* (1955) found that cor pulmonale was present in 16.7%

of 265 cases of heart failure and a majority of the patients with cor pulmonale were performing heavy manual work out of doors, many being farmers.

The effect of heavy cigarette smoking on the prevalence of respiratory symptoms is well known, and is again apparent in the cases of cor pulmonale, though the association is not statistically significant. The present findings agree with the association of heavy smoking with bronchitis found by several authors (Doll and Hill, 1956; Stuart-Harris and Hanley, 1957; Edwards *et al.*, 1959; Higgins, 1959). A similar association between heavy smoking and ischaemic heart disease has been suggested by Hammond and Horn (1954), and among doctors of certain ages by Doll and Hill (1956). Hammond and Horn (1958) and Buechley *et al.* (1958) have confirmed this relationship. Yet no gradation in the prevalence of ischaemic disease in various classes of smokers was found in the Framingham heart study by Dawber *et al.* (1957), and Edwards *et al.* (1959) have recorded a negative relationship between hypertension and smoking. Our own results were on the whole suggestive of a positive relationship between ischaemic disease and smoking habits.

Summary

487 cases of congestive heart failure admitted to hospitals of the Sheffield hospital region were studied during 1955 and 1956. 235 patients were from Sheffield, most of the remainder being admitted to hospitals in Derby, Leicester, and Nottingham. The cases were classified into four groups—cor pulmonale, degenerative, rheumatic, and miscellaneous.

The proportion with cor pulmonale in Sheffield was 41% and in the other hospitals 30%. Hypertension and ischaemic heart disease occurred in 32% of Sheffield cases and in 35% of cases in other areas. Rheumatic heart disease and a number of miscellaneous conditions, such as anaemia, thyroid disease, pulmonary embolism, congenital heart disease, acute infections, carcinoma, and obesity, made up the remainder.

The age and sex distribution of the cases of cor pulmonale indicated a preponderance in males aged 45 to 64, but patients of 70 and over were not included in the study.

The death rate was from 30 to 41% in the various groups of cases, with an overall rate of 35%. The rate for patients with recent myocardial infarction was 46%.

Patients with cor pulmonale had a high incidence of past attacks of bronchitis and of pneumonia and a low incidence of rheumatic manifestations and of anginal pain.

At the time of admission the expectoration of mucopurulent or purulent sputum, drowsiness or disorientation, cyanosis of the lips or tongue, clubbing of the fingers, chest signs suggesting emphysema, and evidence of right ventricular disease occurred to a much greater extent in cases of cor pulmonale than in the other groups of cases. Auricular fibrillation, left ventricular disease, and hypertension occurred in a lower percentage in cor pulmonale than in other cases.

A raised venous haematocrit and high plasma alkali reserve occurred more often in cases of cor pulmonale than in the other groups.

Residence in an industrial environment was commoner in the cor pulmonale cases than was residence in other areas.

Heavy cigarette smoking was associated with both cor pulmonale and degenerative heart disease, but the association might have occurred by chance.

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MANNOMUSTINE IN TREATMENT OF LEUKAEMIAS, POLYCYTHAEMIA, AND MALIGNANT DISORDERS

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Since the introduction of β -chloralkylamines as therapeutic agents for the treatment of leukaemias and the reticuloses (Gilman and Philips, 1946; Wilkinson and Fletcher, 1947) many derivatives and analogues have been examined. Those in more or less regular use at the present time have been considered previously (Wilkinson, 1953, 1955a, 1955b; Scott, 1958). Another cytostatic preparation that has been tried more recently is mannomustine (1:6-bis(β -chloroethylamino)-1:6-desoxy-D-mannitol dihydrochloride; B.C.M.; "degranol"), a substance synthesized by Vargha as one of a series of compounds linking the actively cytotoxic chemical group β -chloroethylamine with a naturally occurring substance, mannitol; it was thought that this would pass more readily through the cell membrane and therefore have a greater selectivity (Vargha *et al.*, 1957).

Mannomustine is a white crystalline compound readily soluble in water, and, although it remains stable for at least 24 hours, it should preferably be freshly prepared

immediately before injection. There are a few reports of the therapeutic trial of this substance by Sellei *et al.* (1956) and by Sellei and Eckhardt (1958) at the National Oncological Institute, Budapest.

Through the kindness of Messrs. Leda Ltd., generous supplies of mannomustine have been made available to us. We report here our preliminary results with this drug in 45 patients having polycythaemia, leukaemias, reticuloses, or malignant disease.

Dosage and Control

Mannomustine was supplied in ampoules containing 50 mg. of the dry crystalline substance; for use the contents of the ampoule or ampoules were dissolved in either physiological saline or ascorbic acid solution (10 g./100 ml.); a convenient strength was 10–20 mg. of mannomustine per ml., although concentrations of 25–40 mg./ml. have been given without the development of thrombophlebitis. It was given intravenously in most cases, but we have also injected the solution intrapleurally when there has been a massive or persistent pleural effusion.

Since the administration of doses as high as 200–500 mg. in one injection led to the much greater frequency and severity of toxic reactions, we later restricted the maximal single dose to 100 mg. daily or on alternate days, and this was found to be the most satisfactory dosage scheme. The required total dosage varied from patient to patient and with the particular disease, as we indicate later.

Diagnoses were made on the usual basis of history, clinical findings, and examination of peripheral blood and bone marrow in the leukaemias and polycythaemia, and in addition by gland biopsy in the reticuloses. Haemoglobin levels and total white blood cell and platelet counts were measured daily and full blood counts at weekly intervals on in-patients and full blood counts were taken at each out-patient attendance.

Chronic Myeloid Leukaemia (12 Cases)

Twelve patients with chronic myeloid leukaemia were treated with mannomustine (see Table I). Nine of these had had no previous antileukaemic treatment, while the remaining three (Cases 10, 11, and 12) had previously received busulphan ("myleran").

In general it was found quite satisfactory to give in single intravenous doses of 100 mg. an initial total course of 800–1,000 mg. when the initial white-cell count was 80,000 to 150,000/c.mm., and of 1,200–1,800 mg. when the initial white-cell count was over 200,000/c.mm. Subsequent doses were determined according to the haematological responses obtained.

In all patients moderate symptomatic improvements were noted, and were usually most pronounced two to six weeks after the beginning of treatment. In five patients this could be attributed partially to blood transfusions given. The livers were enlarged initially in 10 patients, 8 of whom showed moderate or marked reductions in size, maximal reductions occurring within six to eight weeks. The spleens were enlarged in all but one patient (Case 12); there was marked reduction in size in five patients; slight or moderate shrinkage in four others, and the spleen became palpable in only two (Cases 2 and 5). One patient (Case 10) with gross splenomegaly and a white blood cell count of 31,000/c.mm. was given mannomustine in an attempt to reduce the size of the spleen. Only slight reduction