demand for admissions to the unit we referred to tables of Poisson probabilities to determine the frequency of overload with various levels of provision of beds above the calculated average.

There are obvious dangers in generalizing from the experience gained in a sample of the Doncaster population. Nevertheless, the approach to estimating the size of a coronary care unit described in this paper seems to have reasonably wide applicability.

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Acute Myocardial Infarction in Doncaster II—Delays in Admission and Survival

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Summary

The speed of admission of patients with suspected acute myocardial infarction was observed over a period of 12 months during which a "no refusal" coronary care scheme was functioning, with emphasis on minimizing delay. During the same period the duration of survival of cases diagnosed as coronary thrombosis by the coroner's pathologist was measured. Comparison of the two series shows that 75% to 80% of the coroner's cases had died before the median time of notification of the general practitioner by those patients referred to hospital.

We argue that the provision of mobile coronary care on request from general practitioners is unlikely to have an appreciable effect in preventing deaths from acute myocardial infarction outside hospital.

Introduction

It has been known for some time that death from acute myocardial infarction usually occurs in the first few hours after the onset of attack. McNeilly and Pemberton¹ studied survival of patients both in hospital and outside who were certified as dying of coronary artery disease or arteriosclerotic heart disease in Belfast. They showed that the median time of death lay between 3 hours 30 minutes after the onset of attack for men and 6 hours 18 minutes for women. This evidence laid greater stress on the need for speed in the provision of acute coronary care. It was with this in mind that we planned a prospective study of patients with proved or likely acute myocardial infarction in Doncaster (a) to determine the duration of the stages leading to admission to the coronary care unit (C.C.U.), and (b) to measure the survival times from the onset of attack in fatal cases either in hospital or outside and reported to the coroner. Finally, we hoped to obtain some guidance about the possible impact of a coronary ambulance on mortality in Doncaster.

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Method

Patients included in this study were drawn from two sources—(a) admissions in one year to the hospital coronary care unit from 10 selected practices utilizing a "no refusal" service, as described in part I of this paper; and (b) all cases in the same year diagnosed as coronary thrombosis or occlusion at necropsy by the coroner's pathologist in Doncaster. Details, with times, of the events preceding death were obtained in most of these cases from the relatives, general practitioner, or coroner's officer.

Results

ADMISSION TO CORONARY CARE UNIT

Despite attempts to speed up admission of cases described in part I of this paper the median time of admission was 3 hours 22 minutes after the onset of attack. The times of the various stages before admission are shown in Table I.

The greatest delay was due to patients, half of whom waited 1 hour 50 minutes or more before requesting medical assistance. This delay was minimal in 15% who notified within 15 minutes and maximal in 18% who waited eight hours or more. In contrast the ambulance services moved with gratifying speed,

TABLE I—Distribution of Cases by Time Intervals between Onset of Attack of Chest Pain and Admission to Coronary Care Unit

Time Interval (hours)	(1) Attack to C.C.U.		(2) Attack to Notification of G.P.		(3) Attack to Ambulance Called		(4) Ambulance Called to Collection		(5) Collection to Delivery at A.E.D.		(6) A.E.D. to C.C.U.	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
< 1	36	10.3	68	15.0	30	9.3	183	55.1	210	63.3	192	53.5
1 - 1.5	71	20.3	31	6.8	25	7.8	113	34.1	106	31.9	87	24.2
1.5 - 2	53	15.1	64	14.1	39	12.1	32	9.6	16	4.8	53	14.7
2 - 3	41	11.7	78	17.1	51	15.8	4	1.2			22	6.2
3 - 4	18	5.1	42	9.2	41	12.7					4	1.1
4 - 5	15	4.3	32	7.0	18	5.6					0	
5 - 6	15	4.3	25	5.5	17	5.3					0	
6 - 7	11	3.1	9	2.0	12	3.7					1	0.3
7 - 8	11	3.1	15	3.3	7	2.2						
8 - 24	59	16.6										
24 - 48	17	5.1	80	17.6	72	22.4						
48 - 96	5	1.5										
96 +	9	2.6										
Total	350	100	455	100	322	100	332	100	332	100	359	100
Median	202 min*		110 min		143 min		13 min		12 min		14 min	

*Note that the sum of the medians calculated for columns 3, 4, 5, and 6 is different from the median of the measured interval between attack and admission to C.C.U. (column 1). This is to be expected.
A.E.D. = Accident and emergency department.

collecting 89.1% of the patients within 30 minutes and delivering 95.2% within 30 minutes to hospital.

A comparison of the duration of these preadmission stages is made in Fig. 1 by charting their median times derived from Table I. This again emphasizes the relative importance of delays

FIG. 1—Median intervals between onset of attack and arrival in coronary care unit. A.E.D. = Accident and emergency department.

due to patient and general practitioner. Delay in transfer from the accident and emergency department to the coronary care unit emerges as a factor equal in importance to one ambulance journey, even though serious attempts were made to minimize it.

SURVIVAL AFTER INFARCTION

The durations of survival after the onset of acute myocardial infarction are recorded in Table II in 51 fatal cases admitted to hospital and 148 coroner's cases examined during the same period of 12 months. The median times of death were very

TABLE II—Interval between Onset of Attack and Death

Time Interval	Hospital (C.C.U.) Series				Coroner's Series			
	Males	Fe-males	Total	%	Males	Fe-males	Total	%
<15 min	1	1	2	3.9	50	22	72	48.6
15-29 min	0	0	0	0	11	6	17	11.5
30-59 min	0	0	0	0	9	4	13	8.8
60-119 min	1	0	1	2.0	13	2	15	10.1
120-179 min	0	0	0	0	6	1	7	4.7
180-359 min	0	1	1	2.0	7	2	9	6.1
360-719 min	0	0	0	0	2	0	2	1.4
12-23 hr	4	2	6	11.8	3	0	3	2.0
24-47 hr	6	4	10	19.6	3	3	6	4.1
48-167 hr	12	4	16	31.3	1	2	3	2.0
1-2 weeks	4	3	7	13.7	0	0	0	0
2-3 weeks	3	4	7	13.7	0	0	0	0
3-4 weeks	1	0	1	2.0	1	0	1	0.7
Total	32	19	51	100	106	42	148	100
Median	87.67 hr	92.63 hr	88.9 hr		19.1 min	14.4 min	16.8 min

FIG. 2—Survival times after fatal acute myocardial infarctions.

different in the two series—16.8 minutes for the coroner's cases and 88.9 hours for patients admitted to hospital.

The short survival time after myocardial infarction is emphasized in Fig. 2, which uses the same time scale as the figure given by McNeilly and Pemberton.¹

EFFECT OF "CORONARY AMBULANCE" ON SURVIVAL

In Fig. 3 the duration of survival curve of coroner's cases with coronary occlusion is superimposed on the distribution of factors delaying admission to hospital (Fig. 1). It is assumed

FIG. 3—Comparison of survival times of coroner's cases of acute myocardial infarction with median delays in the start of coronary care of hospital cases.

that the rationale of a coronary ambulance would be to provide coronary care for those patients who may die before admission to hospital—that is, those fatal cases at present referred to the coroner. Clearly death had occurred in 79% of the coroner's cases before half of the hospital patients had requested medical aid. The provision of a "coronary ambulance" service to be called by general practitioners would result in advancing coronary care by a fraction of the duration of the patient delivery time (median 12 minutes) at a point where the survival curve is almost horizontal. This would not have a significant effect on saving life.

Discussion

The speed of admission to the coronary care unit after acute myocardial infarction in Doncaster compares favourably with studies elsewhere in Britain. The similarity of the median times of preadmission stages to those found in Edinburgh and quoted by Gambier² (Table III) reflects our intention to follow their admission policy.

Death after the onset of acute myocardial infarction is usually swift. Exactly how swift is shown by Figs. 2 and 3. The fact that the median delay in calling for help by the patient is

TABLE III—Comparison of Admission Times in Doncaster and Edinburgh (Median Times)

Delay	Edinburgh	Doncaster*
Patient	1 hr 44 min	2 hr 13 min
General practitioner	1 hr 34 min	34 min
Ambulance collects	20 min	15 min
Ambulance delivers	21 min	12 min
Transfer from accident and emergency department to C.C.U.	29 min	13 min
Total	4 hr 28 min	3 hr 27 min

*Hospital series only.

1 hour 50 minutes highlights one of the major obstacles preventing coronary care reaching those patients who die soon after the onset of their attack and are referred to the coroner.

Appreciation of the fact that delay can be due to referral through the general practitioner has led to an attempt to bypass primary medical care in acute myocardial infarction in the Belfast coronary care scheme.³ This delay operates in most parts of the British Isles, however, and further separates the patient from coronary care by a median time of 33 minutes in Doncaster.

It seems clear from our results, summarized in Fig. 3, that the provision of a mobile coronary care unit to be alerted by general practitioners cannot be expected to contribute very much to the saving of life after acute myocardial infarction,

especially in an area such as Doncaster, where ambulance delays are minimal.

We acknowledge the enthusiastic and skilled work done by all participants in the coronary care scheme. In addition, we are grateful to Dr. Henry Lederer for reports on necropsies and to Mrs. Jean Durdy, who untiringly supervised the documentation. One of us (H.C.S.) received a research grant from the Sheffield Regional Hospital Board.

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Scientific Basis of Clinical Practice

Adrenal Corticosteroids — Physiological Considerations

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Adrenal cortical function largely depends on the presence of the pituitary adrenocorticotrophic hormone (ACTH). Its action on the adrenal cortex is shown by its stimulatory effect on adrenal weight, histological appearance, and, of course, by its effect on the secretion of adrenocortical hormones. Nevertheless, it is the two inner zones of the adrenal cortex, the zona fasciculata and the zona reticularis, which are primarily dependent on ACTH, though the narrow outer zone, the zona glomerulosa, will also atrophy in time after hypophysectomy.

We now know that ACTH is a straight chain polypeptide containing 39 amino acids. Its biological activity resides in the first 24 amino acids (N-terminal end) and this part of the molecule seems to be common to most species. Immunological activity resides in the rest of the molecule. The biologically active 24-amino-acid peptide has been prepared synthetically and is now available commercially.

Regulation of ACTH Release

The turnover of ACTH in the blood is very rapid (its half-life is about 15 minutes), thus allowing adjustments to changing requirements to be quickly achieved. It is generally believed that, for basal requirements, the secretion rate of ACTH is regulated by a negative feedback mechanism, which monitors the activity of the adrenal cortex by sensing the level of one of the adrenal cortical hormones, cortisol, in the blood. Absence of this hormone, as in Addison's disease, leads to a great increase in the production and release of ACTH. Cortisol is thought to regulate ACTH production by an action on the hypothalamus. This area of the brain is now considered to play an important part in regu-

lating the release of pituitary hormones by means of the production, by various nuclei, of substances called "releasing factors" or "releasing hormones." These substances are released from nerve terminals into the region of the median eminence, whence they are carried to the anterior pituitary gland by the hypothalamic-hypophyseal portal vessels. The factor regulating ACTH release has been called corticotrophin-releasing-factor (CRF), though its structure is still uncertain. Fig. 1 (opposite) shows the relations between the hypothalamus and the pituitary and adrenal glands. Note that, though ACTH stimulates the production of adrenal androgens and aldosterone, these do not play a part in regulating ACTH secretion.

Even under resting conditions the level of circulating cortisol is not maintained at a steady level. There is a definite diurnal variation in the levels observed: lowest values are found at night and highest in the morning (peak values may be five times as high as trough values). This diurnal rhythm is believed to be related to, but not directly dependent on, the subject's sleep-wake pattern of activity. The hypothalamus and pituitary are also concerned in this cyclic variation in activity.

A third and very important factor is the ability of several neural stimuli, usually included in the term "stress," to override the chemical feedback system by directly causing the hypothalamus to modify its rate of secretion of CRF. Thus the hypothalamus, because of its connexions with higher nervous centres, its sensitivity to circulating levels of cortisol, and its ability to influence the anterior pituitary gland, plays a major part in integrating information from the external and internal environment and can, as a consequence, influence the behaviour of the endocrine glands.

Actions of ACTH

Current evidence suggests that ACTH exerts its trophic action on the adrenal cortex by activating a membrane-bound enzyme, adenylyl cyclase. This enzyme, which catalyzes the conversion of ATP to cyclic AMP, is of considerable interest because several hormones act on it at their normal