OBSERVATIONS ON THE EFFECT OF HYDROCORTISONE AND PREDNISOLONE ON CASES OF ACUTE MYOCARDIAL INFARCTION, WITH PARTICULAR REFERENCE TO THE EFFECT ON CONDUCTION DISTURBANCE.

By

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CHAPTER 1.

1. Object and Scope of the work.

(i) Initial observations.

(ii) Rationale for trial of therapy.

(iii) Information sought from work.

2. Acknowledgements.

PREFACE

OBJECT AND SCOPE.

During 1959-60 a number of cases of heart block were treated with oral cortico-steroids, and it was observed that, as reported by others (Prinzmetal and Kennamer (1954); Litchfield et al (1958) and Phelps and Lindsay (1957)) under certain circumstances, the existing block might give way to normal rhythm. Early in 1961 a man (Case E.1) was admitted, gravely ill, with complete heart block as a complication of an acute myocardial infarction. To obtain a more rapid effect and also as treatment for the severe shock, hydrocortisone was given intravenously. Within an hour, the rhythm was normal and the patient comparatively well. Over the next 24 hours, the rhythm lapsed into some degree of block with Stokes-Adams seizures on three occasions. Each time it was possible to restore normal rhythm rapidly by the intravenous administration of more hydrocortisone. This finding indicated a direct relationship between the administration of the steroid and the disappearance of the heart block. A similar regime was used on the next case of heart block admitted following acute myocardial infarction. In this patient, (Case E.2) not only was the heart block resolved in a similar manner, but the acute posterior infarct pattern on the electrocardiogram was no longer detectable after twelve hours steroid therapy. During the withdrawal of steroid therapy the infarct pattern recurred and remained. It was known that in dogs, Johnson et al (1953) had been able, by the exhibition of cortisone to reduce the size of an experimentally induced infarct, and it was felt that

these initial observations would justify a trial of steroid therapy in cases of acute myocardial infarction. During the preliminary period, and in the course of a controlled trial, 25 cases of heart block have been observed. These have been divided into several groups since the therapy was based on different dosage schedules. Apart from this group , 50 cases of acute myocardial infarction which satisfied predetermined criteria, have been divided into a control group and a group treated with hydrocortisone and the results compared. A review of 100 similar cases admitted to the same hospital prior to start of the trial has also been undertaken.

From these results, and the material gained from autopsies, it is possible to comment upon the experimental work performed on animals; on the effect on the cardiogram; on the theories advanced for the mode of action of steroids in heart block, and to assess the value of the therapy in acute myocardial infarction.

A C K N O W L E D G E M E N T S.

This work has been undertaken in the Cardiology Department of the Victoria Infirmary and could not have been done but for the interest and encouragement of Dr. A.A.F. Peel who arranged for the trial of therapy to take place on patients admitted to his wards and who has been a constant source of help and advice. I am grateful also to other members of the Consultant Staff who made their patients available for study, and to my colleagues, house officers and registrars who have assisted in carrying out the trial as prescribed. Several members of the Department of Pathology have advised on the autopsy material and the preparation of microphotographs. Mr. Hugh Gray of Department of Medical Illustration has prepared slides and illustrations.

Dr. R. A. Robb of the Department of Mathematics, University of Glasgow has advised on the analysis, presentation and statistical significance of the results. Miss Margaret Gibson of the Secretarial Staff has typed and retyped each draft with patience, diligence and commendable fortitude.

CHAPTER 2.

1. Historical review of the subject from medical literature.

   (i) Experimental work in animals.

   (ii) Observations in man - clinical reports.

   (iii) Observations in man on untreated heart block.

   (iv) Theories of the mode of action of cortico-steroids in heart block:

      (a) Prinzmetal (1954).

      (b) Lown (1955.

      (c) Freidberg (1960).

2. Preliminary studies on which trial was based.

   (i) Oral steroids.

   (ii) Parenteral therapy.

HISTORY.

In 1942 the use of adrenocortical steroids for the treatment of shock was introduced (Shleser & Asher). Although initially used in acute surgical collapse and shock (Cole et al 1953) their use in cardiogenic shock was under consideration. Theoretically the twin side effects of salt retention and interference with normal scar formation, appeared to be obstacles to the use of cortisone in coronary artery disease, particularly in the presence of acutely injured myocardium following myocardial infarction. In an attempt to find out whether cortisone could be given in the presence of an acute infarction, Chapman et al (1952) conducted a series of experiments on dogs; they were able to show that cortisone in a dose of 7 mgm/kgm. did not delay healing after a surgically induced infarct.

Following this, Johnson et al (1953) in a carefully contrived series of animal experiments showed not only that the cortisone caused no undue delay in infarct healing in doses of 12.5 - 20 mgm., b.d., but also that the cortisone treated animal had a significantly smaller infarct than a "paired" control. Two groups of experiments were performed. In group I an infarct was induced by ligation of the anterior descending branch of the left coronary artery 1.5 cm. below the origin of the circumflex branch. Seven pairs of animals were used. The average weight of the control animals was 30 kgm and of the treated animals 33 kgm. The corresponding mean heart weights were 104 gms and 109 gms. The size of the infarct averaged 7.88 c.cm. in the control animals as opposed to 0.96 c.c. in the cortisone treated animals.

TABLE 1.

Johnson et al (1953).

	Low Ligation		High Ligation	
	Control	Treated	Control	Treated
Average Weight (dogs).	30 Kgm.	33 Kgm.	35.8 Kgm.	36.2 Kgm.
Average heart weight.	104 gm.	109 gm.	117.1 gm.	119.2 gm.
Average Size of infarct.	7.8 cc.	0.96 cc.	18.8 cc.	0.14 cc.

In a second group of 9 pairs of dogs, in which the left coronary artery was ligated 0.5 c.m. below the origin of circumflex branch, the comparative figures were equally striking. The control animals (35.8 kgm) showed on average an infarct of 18.83 c.c. in a heart of 117.1 gms. While the treated animals (36.2 kgm.) had on average an infarct of 0.141 c.c. in a heart weighing 119.2 gms (Table 1). X-ray studies after injection of the coronary vessels with barium chloride demonstrated an increase in intercoronary capillary anastomoses in the treated animals as compared with the control. In a third group of 12 animals, 4 were pretreated with Adrenocorticotrophic Hormone (A.C.T.H.) and 4 with cortisone for one month prior to the infliction of an identical myocardial injury. In this series, radio-opaque dye injected into left coronary artery demonstrated increased capillary anastomoses in the treated animals. In some of them the dye appeared in the right coronary tree also, but this never occurred in any of the control group. Finally, 57 animals had a major infarct produced surgically and the survival of cortisone treated and control animals was compared over the succeeding 72 hours. In the control group 18 animals died out of 34 - a mortality rate of 53% as opposed to 22% (5 animals of 23) in the treated group.

It was natural that this work should stimulate others, and in 1953 a further series of similar experiments on dogs was published by Opdyke et al. They were unable to confirm the findings of Johnson et al but it is only fair to state that their experiments were not so carefully controlled as those of the former authors. In their two groups of animals, high dosage

(10 mgm/kilo, cortisone) and low dosage (3 mgm/kilo, cortisone) schedules were compared with control animals. The animals were not paired for weight or for heart size. The site of ligation of left coronary artery varied from 9 mm. to 34 mm. from mouth of the vessel, and in one case no infarct was found at autopsy.

Hepper et al (1955) tried a smaller number of experiments on dogs using high and low dosage regimes similar to those of Opdyke. They were principally concerned with rate and progress of healing, and showed that while there was narrowing of the band of "tissue reaction" round the infarcted area, which might be taken as an advantage, there was appreciable delay in phagocytosis of the necrotic muscle. This was also observed by Johnson et al (1953) up to the fourteenth day after infarction but their work suggested that by the 30th day there was sound healing, and they noted no appreciable difference between the healing in control and treated animals. This is in agreement with the earlier report of Chapman et al (1952).

At this juncture, attention was transferred from animal experiments to human use, when Prinzmetal and Kennamer (1954) used corticotrophin intramuscularly in a patient who had complete heart block as a complication of myocardial infarction. Normal rhythm was restored; and when the block recurred later, a further injection was again effective, thus largely ruling out coincidence. They postulated an anti-inflammatory effect as the mode of action of the corticotrophin. The following year (1955) Lown et al pursuing another aspect of this subject first mooted by Somerville, Thorn and Levine (1951), contrasted cardiograms of 50 cases of Addison's dease, 39 cases of Cushing's syndrome and 539 control subjects to illustrate the effect of

TABLE 2.

PROGNOSIS IN COMPLETE HEART BLOCK.

REPORTED CASES.

	Total	Early Death	Survived 1/12 +
Fulton 1925.	2	2	0
Bell & Pardee 1930.	1	0	1
Sanders 1931.	1	1	0
Hausen 1932.	1	1	0
Ball 1933.	1	0	1
Boas 1933.	1	1	0
Rothschild 1933.	1	0	1
Schwartz 1933.	4	2	2
Addey 1934.	1	0	1
Schwartz 1936.	15	4	11
Kerr 1937.	5	2	3
Master et al 1938.	6	4	2
Penton et al 1956.	49	21	28
Condry & Thompson 1957.	14	9	5
Gilchrist 1958.	25	11	14
Rowe & White 1958.	38	16	22
	166	75	91

MORTALITY = 45%.

too little and too much steroid. They observed a mean P-R of 0.176 (range 0.14 - latent block) in Addison's disease; a mean P-R of 0.136 (range 0.12 - 0.18) in Cushings syndrome as opposed to a mean of 0.158 (range 0.13 - 0.20) in normal subjects. They postulated a "facilitating" effect of steroids on the conducting mechanism in the heart. No relationship could be established between electrolyte levels and the rate of conduction in this series of experiments.

The need for further examination of Prinzmetal's treatment of heart block was emphasised by reports on series of cases of complete heart block by Penton et al (1956), Condry and Thomson (1957) and Gilchrist (1958). Gilchrist emphasised that while the prognosis for those surviving the acute stage was relatively good, and return of the original rhythm might be anticipated in 7-10 days, the immediate mortality was high. A survey of published cases shows in fact an immediate mortality of 45% (Table 2). A report of a case of acute infarct in which complete heart block was restored to sinus rhythm nine hours after injection of corticotrophin (Phelps & Lindsay, 1957) lent emphasis to Prinzmetal's claim; and the rapidity of action might be considered especially valuable in view of the high immediate mortality. The ability of steroids to banish the Stokes-Adams seizures which frequently accompanied heart block was also observed, and in subsequent publications this useful effect was confirmed (Litchfield et al, 1958; Caramelli & Tellini, 1960; Aber and Wynn Jones, 1960; Friedberg et al, 1960; Pay & Earl Waverley, 1961). During this period the interest has been focussed mainly on the cessation of Stokes-Adams attacks, since this occurs even when in heart block of long standing which persists during steroid

TABLE 3.

EFFECT OF DURATION OF BLOCK ON RESPONSE TO TREATMENT.

Author	No. Cases.	No. Recent Infarct.	Effect on Block	Time Taken.	Preparation Used.
Prinzmetal & Kennamer.	1	1	Sinus rhythm with recurrence treated successfully.	hours	I.M. Corticotrophin
Phelps & Lindsay.	1	1	Sinus rhythm	9 hours.	I.M. Cortisone 100 mgms.
Rosenfeld & Segall.	3	1	1 only given Steroids - Sinus rhythm.	-	I.M. Cortisone.
Friedberg et al.	6	3	4 achieved sinus rhythm. Recurrence 3. Not restored again.	6-36 hrs.	Prednisolone, oral, 40 mgm. daily.
Aber & Wynn Jones.	5	2	3 achieved Sinus rhythm.	6 hrs - 7 days.	A.C.T.H. I.M.
Pay & Waverley.	8	2	2	-	Oral Predniso-:lone, 80 mgm. per day.
Caramelli & Tellini.	19	7	Sinus rhythm in 5.	4 - 5 days.	I.M.
Dall & Buchanan.	11	7	Sinus rhythm in 6.	36 hrs - 8 days.	Oral Predniso-:lone, 30 mgms per day.
Dall & Buchanan.	7	6	Sinus rhythm in 6.	24 hrs.	I.V. steroids.
	61	30	29		

NOTE: Of 30 cases of recent onset of Block - 27 were restored to sinus rhythm 90%.
Of those cases not of recent onset only 2 reverted to sinus rhythm. 6.6%.

therapy. As there is less urgency in chronic block, oral therapy has tended to replace the intramuscular injection (Aber & Wynn Jones, 1960; Pay & Waverley, 1961). Maintenance steroid therapy has been suggested because recurrence on stopping treatment was observed (Friedberg, 1960; Pay & Waverley, 1961). Since many of the cases were of long standing, little anti-inflammatory action could be anticipated and the "facilitation of conduction" theory of Lown et al gained support although it was suggested by Friedberg (1960) that increased sensitivity of the A-V mode might be the primary effect, and he is supported by others (Caramelli & Tellini, 1960; Pay & Waverley, 1961). In some cases, however, normal conduction was achieved and maintained. This effect can be observed almost exclusively where there has been a recent infarct, and the conduction disturbance is of recent origin (Table 3). In a preliminary report (Dall and Buchanan, 1961) it was shown that in 7 cases of complete heart block following myocardial infarction treated with oral therapy, return of sinus rhythm occurred in periods varying from 36 hours to 8 days. Although there appeared a direct response to therapy, the difference between these results and the rate of spontaneous recovery (6 to 16 days) (Gilchrist) was not sufficiently distinct to draw a firm conclusion on the value of steroid therapy. On the other hand, a group of similar cases associated with recent cardiac infarct and treated with intravenous steroid therapy recovered normal rhythm within hours, and had an improved survival rate (Dall & Buchanan, 1962). It was observed during this work that not only could normal atrio-ventricular conduction be restored where heart block existed, but that co-existing bundle-branch block (right or left) dating from the infarction, was also banished. Improvement in the

cardiographic pattern was so striking in one case in particular that it was argued that there must be an effect on the infarct site, in addition to improvement in conducting mechanism. In the light of known work, an anti-inflammatory effect as described in the animal experiments and postulated in man, by Prinzmetal seemed a reasonable explanation. If this could be achieved in patients with heart block resulting from acute myocardial infarction, it might be possible in cases of acute myocardial infarction without conduction defect to produce similar improvement. This might be expected to result in reduced mortality rates, smaller areas of infarction, improved capillary anastomoses in the myocardium, and presumably a reduction in post-infarct morbidity.

CHAPTER 3.

STRUCTURE OF WORK.

1. Conduction disturbances following myocardial infarction.

   A. Heart Block.

      Diagnosis.

      Standard regime of observation.

      Treatment schedule.

      Use of other drugs.

   B. Bundle-branch block.

2. Trial of Therapy in acute myocardial infarction.

   A. Method of Selection.

   B. Criteria for admission to trial.

      E.C.G. diagnosis.

      Supplementary evidence.

      Treatment regime - Steroid Group.

                         Control Group.

STRUCTURE OF TRIAL.

1. Conduction disturbances following myocardial infarction - heart block.

When any organic lesion or functional disturbance impedes conduction through the bundle of His or through its main branches, the resultant disturbances of rhythm can be termed heart block. This may vary from a prolongation of the P-R interval in the cardiogram (latent block); a fixed atrio-ventricular ratio with dropped beats (partial block); to a complete dissociation of auricular and ventricular activity (complete heart block).

Disturbance of conduction in the branches of the bundle of His does not affect A-V conduction, but rather the intra-ventricular component of conduction causing distortion of the QRS complex in the cardiogram (bundle-branch block). The resultant pattern depends on whether the right or left branch is affected, and the cardiographic appearances of each are characteristic.

The conducting tissue may be disturbed as a result of an acute lesion (e.g. myocardial infarct) or of a longstanding process (e.g. previous coronary thrombosis or arteriosclerotic change). The effect of steroid therapy has been observed on cases of heart block of recent onset and of longstanding.

Chronic (longstanding) Heart Block.

Six cases have been treated with steroids and the results of therapy observed where complete block or a degree of block did not arise from a recent myocardial incident, although it was associated with coronary artery disease in four.

Acute (recent onset) Heart Block.

1. Seven cases of acute infarct with block have been observed on oral steroid therapy, and the response to treatment described in a preliminary report (Dall & Buchanan, 1961).

2. Nine cases of block following acute infarct have been treated with intravenous steroid therapy.

3. Two cases, one admitted before this work was started, and one case of acute block, not recognised, and therefore "untreated" have been observed to provide examples of natural outcome.

4. One case of latent heart block occurred in a steroid treated case and reversion to normal conduction occurred without altering the regime.

Bundle-Branch Block.

During this study bundle-branch block has occurred in seven cases. Left bundle-branch block in one treated case (E.1) and in one control (B.13). Right bundle-branch block in five treated cases (E.4, E.9, F.6. A.6 and A.8). Three of these were known to be of long standing (B.13, F6 and A.8), three of recent onset (E.1, E.4 and E.9) and one in which the time of onset could not be determined.

All except the control case (B.13) had steroids, four in the heart block series, with high doses, and two in the treated group of the trial.

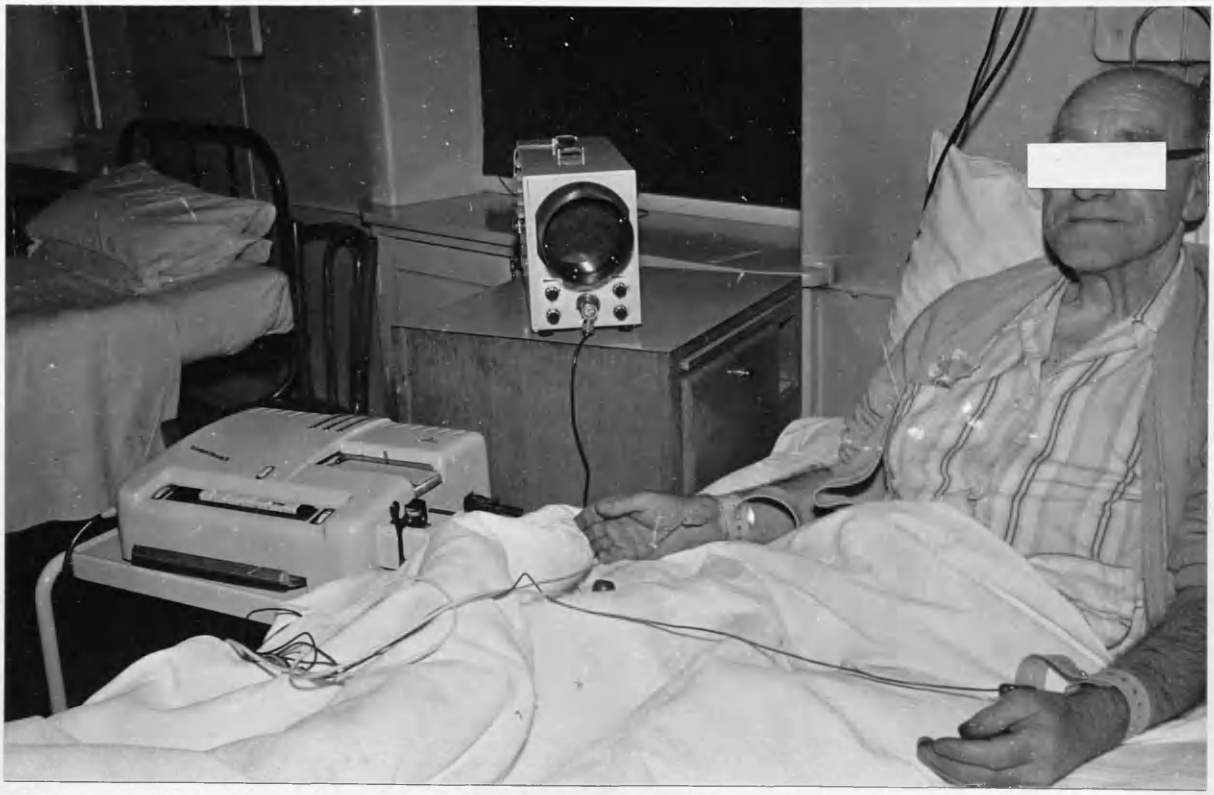
Diagnosis.

Sinus bradycardia may accompany cardiogenic shock and a pulse rate of under 50 per minute cannot be considered a reliable diagnostic feature of complete heart block. In all cases the diagnosis was established by cardiogram. This was particularly important since in heart block

following myocardial infarction, pulse rates of 50 - 60 per minute may be observed (Ball, 1933; Gilchrist 1958), and indeed in two of the present series the diagnosis of heart block was not obvious until the cardiogram was inspected. As it is our practice to record the cardiogram on admission in all cases of suspected myocardial infarction, the diagnosis was not delayed unduly in any of these cases despite the atypical pulse rate.

Standard regime. After clinical examination of the patient, a twelve lead cardiogram was recorded on a portable Cambridge direct writing machine. All records were taken on portable machines so that they might be more easily compared, and there would be uniformity of size for mounting. This had additional advantages in that the machine could be retained at the bedside and serial records could be obtained during the course of treatment. The machine is simple in construction, and once the leads were connected to the patient and the desired standardisation set, it was possible to record serial lengths of lead II at intervals over long periods by instructing nursing staff to switch on the machine for sufficient time to inscribe 12 complexes. Despite the simplicity of this arrangement, as patients were monitored by E.C.G. during the first 24 hours under treatment until a stable sinus rhythm was present, there was much wastage of recording paper; and considerable time was expended in extracting the small sections required to illustrate the phases of recovery from the long records. To reduce this to a minimum, a two channel Oscilloscope was coupled into a portable E.C.G. circuit and by this means monitoring of the degree of block present and of response to therapy could be continuous, while permanent records could be taken when desired. This technique entailed

PLATE 1.



Portable Cardiograph on trolley with
Oscilloscope mounted on locker.

supervision by medical staff, or cardiographic technicians since it could not be left to nursing staff to decide when an alteration in the pattern worth recording had occurred. Nevertheless, it was found preferable to the tedious task of reviewing several complete rolls to select representative pieces for mounting in case reports, since records were taken only of important features, or to illustrate points of specific interest.

The apparatus was light and easily transported to the patient's bedside on a small trolley designed to take the portable cardiograph machine (Plate I). Technically there was one difficulty in the use of the combined machine. When standardised for cardiograph recording, the amplitude was too great for the Oscilloscope channel, and a modification of the standardisation setting was required when switching from oscilloscope to cardiograph and vice versa. This resulted in some slight variation in complex size due to differing standardisations, until we became familiar with the apparatus and more adept at setting and resetting to identical standards; but as the rhythm and the duration of the P-R interval was the chief interest, size of complexes did not affect the value of the records.

In the cases of heart block, the therapeutic regime was initiated as soon as the diagnosis was confirmed by the cardiogram. In this group of cases, therapy was designed to achieve normal conduction as soon as possible. In the absence of any reference to intravenous therapy in this context in published work, the dose of steroids used has been empirical. Working on the assumption that in the presence of an acute injury to the heart, a conduction disturbance which is related to the injury may be

expected to resolve with the exhibition of steroids, the dose of intravenous hydrocortisone was built up steadily in each case until the desired effect was achieved. Thereafter, such hydrocortisone as was required to maintain normal conduction and avoid recurrence was given for the remainder of the first 24 hours, and oral therapy was instituted the following day. The total dosage used ranged from 450 mgm to 700 mgm hydrocortisone given intravenously within 24 hours. In view of the large doses of steroids in use, it was felt that a graduated course of oral prednisolone starting from 30 mgm daily, should be given during the next fourteen days, to wean the patient off steroids. A.C.T.H. was given by intramuscular injection on days 15 and 16. It has been said by Caramelli & Tellini (1960) that this "weaning" process is unnecessary, and that steroids can be stopped when stable rhythm is restored; on the other hand Friedberg (1960) observed steroid-resistant recurrence of block after discontinuing therapy in 3 of 4 cases who had been successfully restored to sinus rhythm and therefore favoured a maintenance dose. In the present work recurrence has not been a feature, but a middle course has been steered and a short, fixed, "weaning" regime has been given irrespective of amount of steroid used in the acute stage.

Technique:- The therapy was initiated by a single injection of 100 mgm of hydrocortisone intravenously and the effect of this was observed for 1 hour. An intravenous infusion of 5% dextrose in water containing 100 mgm of hydrocortisone in 540 ml. was then started. By this means, it was felt that an even background level of steroid might be achieved, with augmentation as required by additional hydrocortisone injected into the tubing of the infusion, at intervals determined by the clinical response. Although

the primary object is the restoration of sinus rhythm within the first 24 hours of therapy, the weaning regime has been designed to extend beyond the fourteenth day, since it is suggested by the animal experiments that there is an appreciable histological difference between "treated" and control animals up to this point, and any anti-inflammatory effect that may be achieved will be obtained during the early stages of healing and repair after myocardial injury.

Other Therapy.

The cases were being treated not only as cases of heart block, but also as cases of acute myocardial infarction. In all cases anticoagulant therapy was given from the onset. Where indicated by the clinical findings aminophylline and diuretics were given. No pressor agents were used.

2. Trial of Therapy in Acute Myocardial Infarction.

As the prospect of conducting a trial in paired cases, treated and control, is almost impossible because of the vast permutation of features that may occur in coronary artery disease, it was decided to collect 50 cases of acute infarction, and allocate them as they presented, to either a "Control" series (Group B) or "Treated" series (Group A) according to a sequence of random numbers. Accordingly, a series of envelopes numbered from 1 - 50 was prepared and a card bearing "control" or "hydrocortisone" was sealed in the appropriate numbered envelope, as dictated by the random number series. This work was undertaken by a secretary so that the trial could remain "blind" to the medical staff until such time as a case was committed to the trial, and an envelope opened. The envelopes were used in strict rotation according to the order of admission of the patients to the trial.

Criteria:- 1. Since the effect sought, was the influence of steroids on freshly damaged myocardium, the trial was confined to cases of myocardial infarction in whom the infarct could be presumed to be not more than 48 hours old. This excluded cases with a history of pain for several days prior to admission, unless there was clear evidence that the early pain was anginal in nature and a striking episode, clearly indicative of infarct had occurred within the 48 hours prior to admission.

2. In all cases a cardiogram was recorded as soon after admission as possible. Patients were not admitted to the trial unless there was positive evidence of infarction, or injury in the cardiogram, or failing this, a typical description of infarct pain associated with clinical findings in keeping with cardiac injury. In this context, the character of the pain, pericardial friction, sudden heart failure, shock and arrhythmia of sudden onset in absence of other causes for these features were considered important. It was decided that to accept only cases with incontrovertible cardiographic changes might exclude two groups of cases, viz. those with the slowly evolving E.C.G. pattern (e.g. Case A2) and those with previous infarct, in whose cardiogram the presence of old injury pattern could make interpretation difficult. As it transpired no fewer than 10 cases (20%) had previous infarcts and 12 had a convincing history of angina varying in duration from 3 months to 3 years; in all of these some pre-existing change in the cardiogram might be anticipated to obscure the changes due to fresh infarction.

For similar reasons, it was decided that the absence of "Q" wave changes in the cardiogram should not invalidate the diagnosis, since changes

in the RT segment and T wave frequently preceded the appearance of abnormal Q waves by some days (Myers and Talmers, 1955; Papp and Smith, 1955; Schlant et al, 1954). Serial cardiograms were recorded every second day during stay in hospital for all cases. Provided the E.C.G. pattern evolved to a "QS" pattern of significance, this was considered as a major infarct. Where a qR or RT pattern was the maximum abnormality, a minor infarct was considered to have occurred although one patient with a "minor" infarct died five days after admission with no further alteration on the cardiogram.

In one case no cardiogram was obtained, as at the time of admission it was not possible to undertake the record, and despite therapy the patient died less than 2 hours after admission. In this case the clinical findings were convincing and the patient was entered in the trial and the regime commenced although the cardiogram was not yet taken.

During the period of the trial three patients were admitted with severe shock and collapse associated with atypical pain, or absence of pain as a symptom. All three died soon after admission to hospital and before a diagnosis was established. Apart from these, there were no deliberate or accidental exclusions from the trial.

Supplementary Evidence. Serum transaminase investigation was not undertaken routinely, but where the cardiographic evidence of fresh infarction was in doubt, for example where a former infarct obscured the changes, confirmation of the clinical impression was sought by biochemical examination. The presence of cardiographic change, or of fluctuation in the cardiographic appearances was taken as evidence of myocardial injury even in the absence

of a significant transaminase level when a discrepancy existed. The Serum Glutamic Oxalacetic Transaminase and Serum Glutamic Pyruvic Transaminase activity were measured on at least two occasions when "Transaminase" estimation was undertaken.

Regime for Trial Cases. Provided the criteria were satisfied, the case of myocardial infarction was allocated to the control group (B) or to hydrocortisone group (A) according to the card contained in the envelope corresponding to the patient's number in the trial. The method of administering the hydrocortisone dictated the form of the regime. Therapy was started by an initial injection of 100 mgms intravenously in 2 ml. followed by a further 100 mgms which was added to a bottle of 5% dextrose in water (540 ml.) and infused intravenously over the next 8 - 12 hours. It was intended by this method to provide in the early stages a constant steroid effect. This was followed on the second day by oral prednisolone, 30 mgms, daily and thereafter a graduated reduction in dose was effected over 14 days, similar to the regime employed in the cases of heart block.

In the cases allocated to the "Control" group, no initial injection was given, but a 5% dextrose infusion identical to the other group was given as slowly as the apparatus would allow. This usually took rather more than eight hours, which meant an infusion of 1 ml. per minute, or less, a rate which was unlikely to cause cardiac embarrassment. There were some misgivings as to the risk of causing left ventricular distress with this infusion, but where there was evidence of left ventricular failure or embarrassment, such as basal rales or triple rhythm, a diuretic of the thiazide group was given intravenously and the infusion was delayed for 1 hour. In those

cases in which acute left ventricular failure did occur, the difficulty did not develop during the infusion but several days later, and did not seem to be directly attributable to the fluid load.

Digoxin, quinidine, procaine amide and aminophylline have been used as required by the clinical findings, in addition to diuretic therapy with thiazide or mersalyl. The only exclusion from the therapeutic regime was the pressor groups of drugs, of whose value in cardiogenic shock, we are not convinced.

Object of Trial.

To see whether the anti-inflammatory properties of steroid hormones, by acting on the area of reaction on the periphery of an infarct would:

1) Reduce the size of infarct.

2) Hasten the evolution of the infarct pattern.

3) Improve the mortality rate.

and to see whether the effects of steroids on conduction described by other Authors, could be verified.

CHAPTER 4.

RETROSPECTIVE SURVEY OF CASES OF SIMILAR NATURE.

Modification of criteria for this work.

Use of parallel data to check validity of "Control" group.

1. "Survey of Similar Case Reports".

In addition to the 50 trial cases, records of 100 other patients who would have satisfied the trial criteria have been studied (Group C). These are patients admitted to the same hospital in the six months preceding the start of the trial. This survey had a double purpose. It was intended to extract from it a "standard" mortality rate for acute myocardial infarctions treated at this hospital, so that the mortality rate of the "control" group (B) in the trial might be compared with this figure, to determine whether intravenous therapy had any harmful effect. The second purpose was to assess the prognostic value of specified features to permit grading of cases into mild, average and severe; it would then be possible to ascertain whether the groups were comparable in respect of severity.

Case records of more than 400 patients admitted with some form of coronary artery disease were reviewed to obtain 100 cases of myocardial infarct which satisfied the trial criteria. One modification was made. Four cases with adequate historical, clinical, biochemical or autopsy evidence of fresh infarction were admitted and died before a cardiogram was taken. Since this would have been recorded on admission for the trial cases, it was felt that these cases should not be excluded from the survey on this count.

CHAPTER 5.

CARDIOGRAPHIC STUDIES.

1. Machine.
2. Technical points arising from type of machine used.
3. Difficulties arising from electrode positioning and influence on interpretation of cardiogram.

E.C.G.

1. Rhythm.
2. A-V conduction time.
3. QRS abnormalities of intraventricular conduction.
4. QRS abnormalities due to infarction.
5. Assessment of rate of evolution.

Cardiographic Studies.

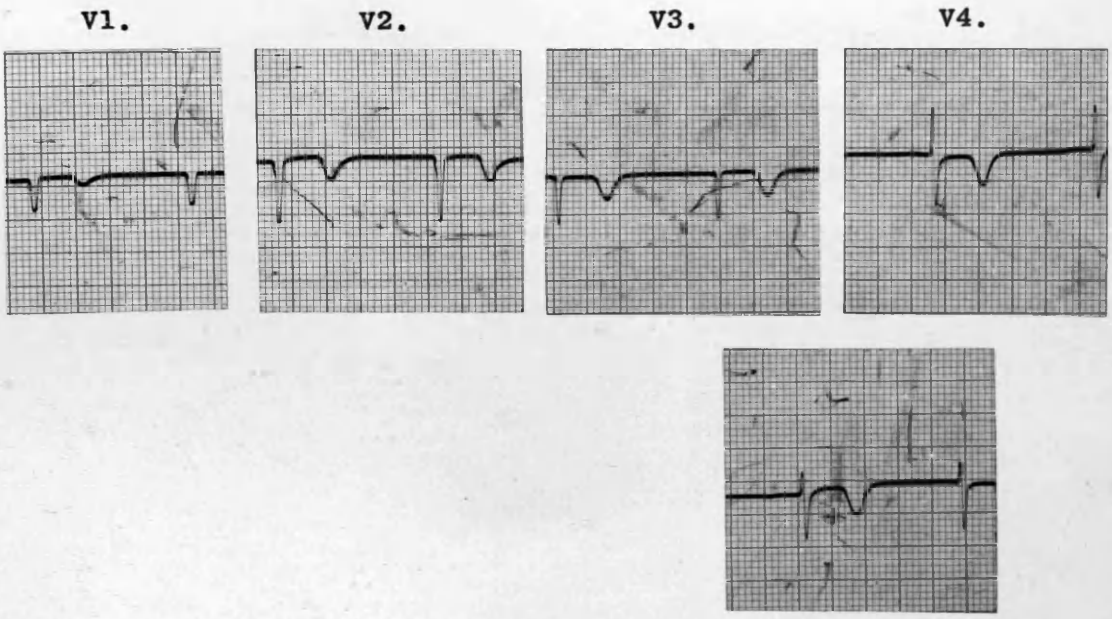
The efficiency of the portable cardiograph is well established in clinical practice. These machines may inscribe the record directly onto moving paper by means of a stylus and ink, or by means of sensitised paper and a heated stylus. The latter type of apparatus is favoured in this hospital, although it has certain disadvantages for routine use, the principal of which is difficulty in mounting the records satisfactorily without smudging or marking the sensitised paper surface. Technically there may be some inertia due to the friction between the stylus and paper which interfers with the sensitivity of the record, but as all records were taken on the same type of machine, this factor will cancel out when comparison of features of the tracings is undertaken.

Reproduction of the records obtained is also more difficult than would be with galvanometer machine records, but the advantages of a light portable and therefore readily available instrument were considered to outweigh this disadvantage in circumstances where many of the cases would be admitted after normal "working hours" and the initial E.C.G. taken by the medical staff on duty. To be comparable, all records were therefore taken on portable apparatus.

A standard 12 lead cardiogram was recorded on admission and every second day thereafter until discharge from hospital, or prior death. Since these records were being compared minutely for changes, it rapidly became apparant that minor differences in the positioning of the chest piece electrode when taking records of leads V1-V6, could alter the appearance of one of these leads quite readily. For example, if an infarct pattern

PLATE 2.

Variability of chest lead complexes with positioning of the electrode.



Alteration in character of QRS produced by shift of electrode V3 one width ($\frac{1}{2}$") towards position of V4.

extended from lead V1-V3 and on the initial records lead V4 was normal, then an abnormality in lead V4 in the subsequent records could be caused by:

1) Extension of the area of infarct, or
2) By placing the chest piece $\frac{1}{2}$" nearer V3 than on the previous occasion (Plate II).

Naturally the converse applies and an apparent improvement of lead V3 might be suggested if the electrode when positioned to record V3 were placed $\frac{1}{2}$" beyond its former site towards V4. In an effort to avoid this fallacy in interpretation, the positioning of leads V1-V6 was routinely marked on the patient's chest with daubs of carmine. While this was comparatively successful in male patients, it was less so in females because the overlap of breast onto the chest wall and the habits of normal hygiene of this area resulted in rapid obliteration of the marks. Since frequent records were being taken, it was decided that where possible the patient should have his or her cardiogram performed by the same technician on each occasion, thus reducing the likelihood of minor difference resulting from differing techniques. In interpretation, a single lead was not considered to be altering unless the change was present on two consecutive records. While this might mean delay in recognising a minor change in a single lead during the course of the trial the date of such a change could be accurately determined at the completion of the trial by reference to the preceding and following records. By these measures reasonable accuracy in recording and interpretation of the records was achieved.

The cardiogram was examined for each of several features.

Rhythm.

The interest lay in arrhythmias, and in the fate of any abnormal rhythm in the control group as compared with the treated cases. Interest had been sharpened by the observation that in one of the cases of heart block which showed the rare combination of auricular fibrillation and heart block (Case E.4) following acute infarct, fibrillation disappeared soon after the initial hydrocortisone injection.

The effect of treatment was observed in one other case of auricular fibrillation of recent onset, and in one case of long standing fibrillation. These are discussed in detail in Chapter 8.

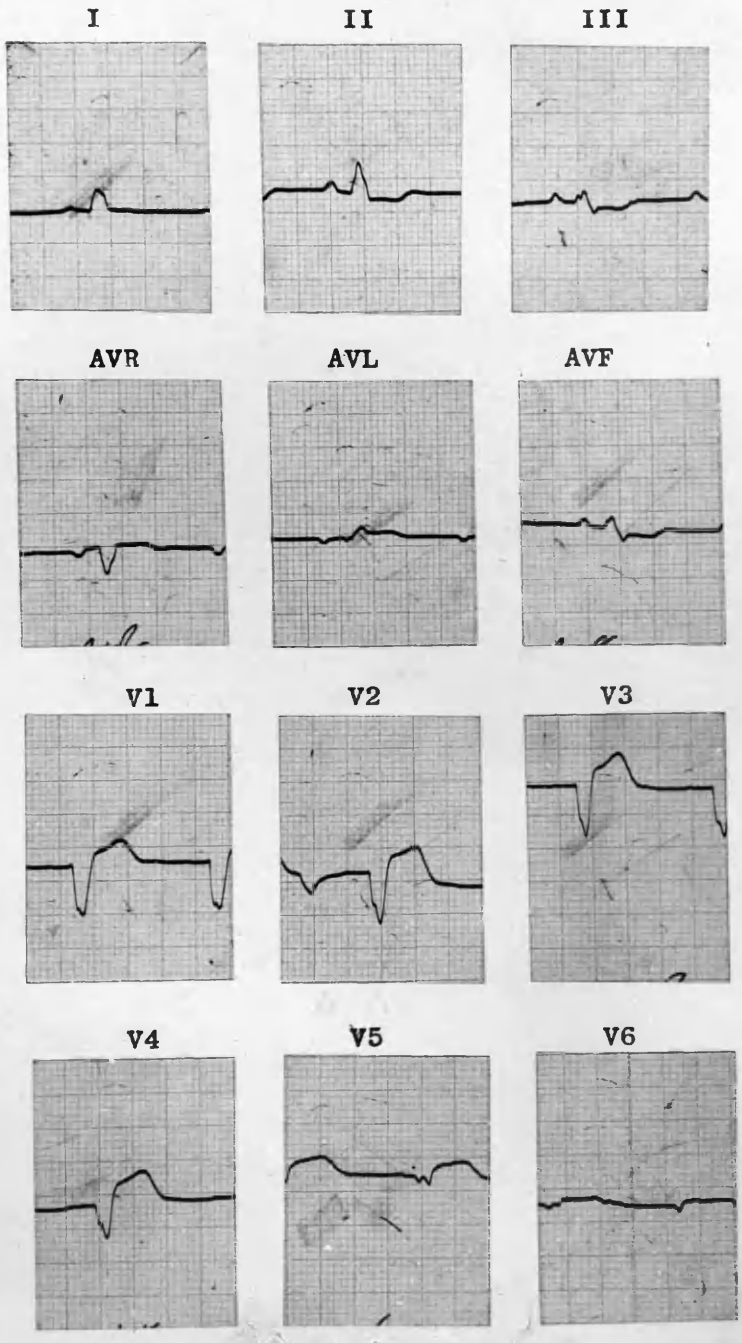
Conduction.

One case of latent block and one of complete heart block occurred in the treated group. A modification of the prescribed regime was made to give further hydrocortisone to the complete block. No case of atrio-ventricular conduction disturbance occurred in the control group.

In view of Lown's work (1955) and the supporting evidence of Caramelli and Tellini (1960) it was decided to observe the effect of the steroid course on the P-R interval. This segment was measured in Lead 2 of the initial cardiogram and at the end of the first week of therapy (i.e. in the middle of the steroid regime), and again in the last cardiogram prior to discharge, by which time the patient had been off steroids for at least two weeks.

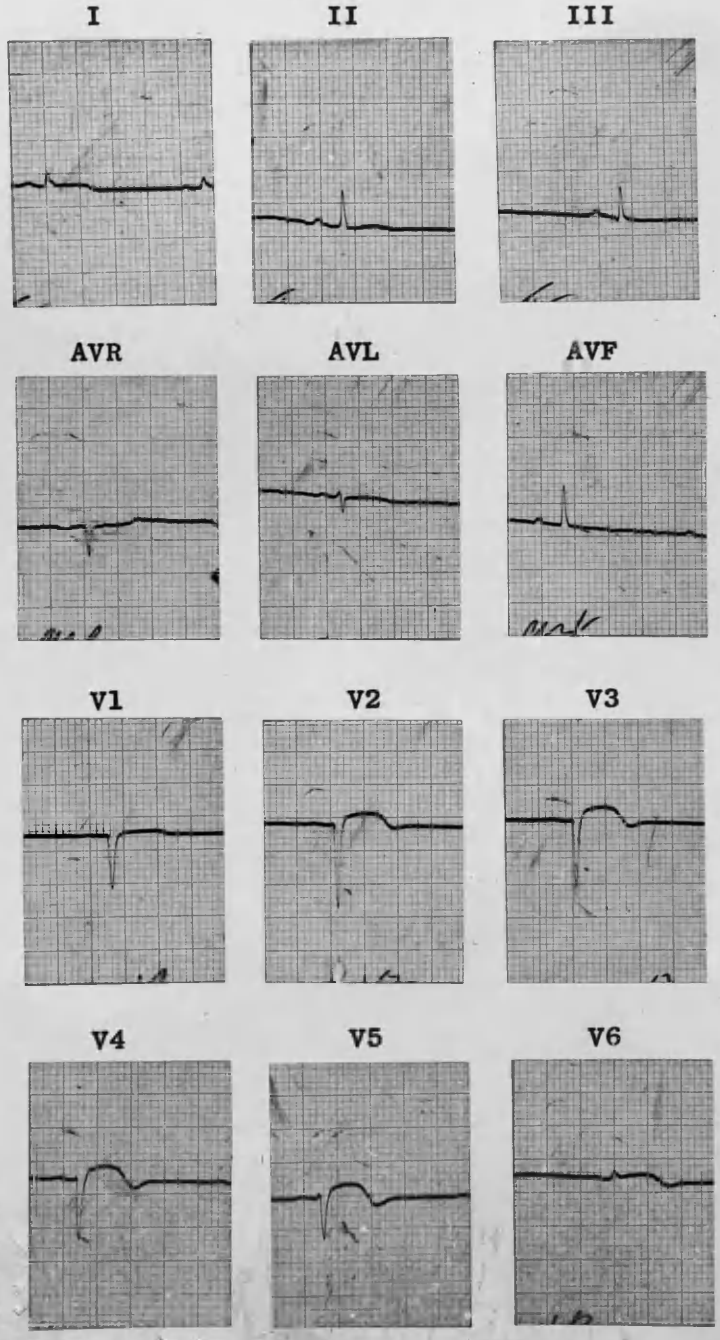
Bundle-branch block was observed in three cases in the trial, and in three others of the heart block series. Of the trial cases, one case in the control group with left bundle-branch block and one in the treated

(a) (1) BUNDLE BRANCH BLOCK AFTER RESOLUTION OF COMPLETE BLOCK. E.C.G. 728/61.



J.S. (Case E.1.) PLATE 3a.

(b) BUNDLE BRANCH BLOCK RESOLVED AFTER 8 DAYS PREDNISOLONE, SHOWING ANTERO-SEPTAL INFARCT.



(a) CARDIOGRAM TAKEN ON PREVIOUS ADMISSION (MAY 1961) SHOWING EXISTING L BUNDLE BRANCH BLOCK PATTERN.

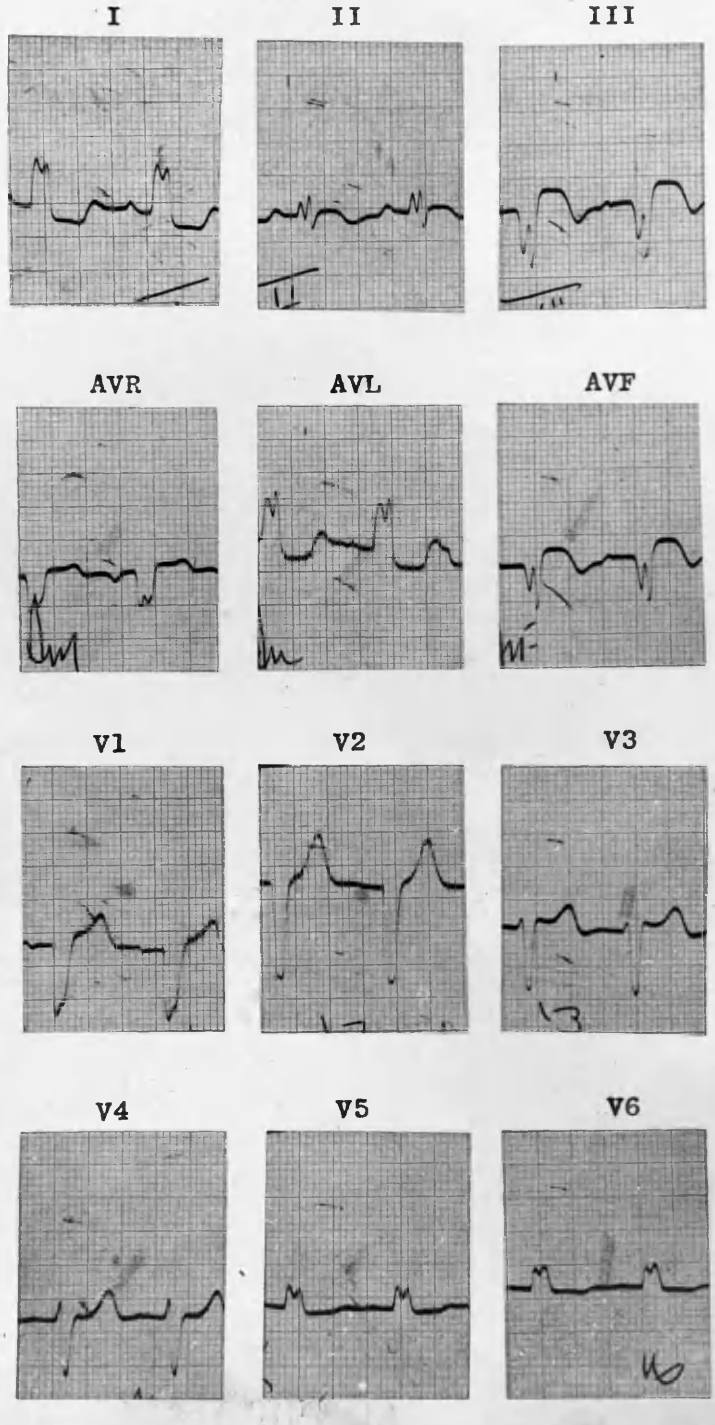
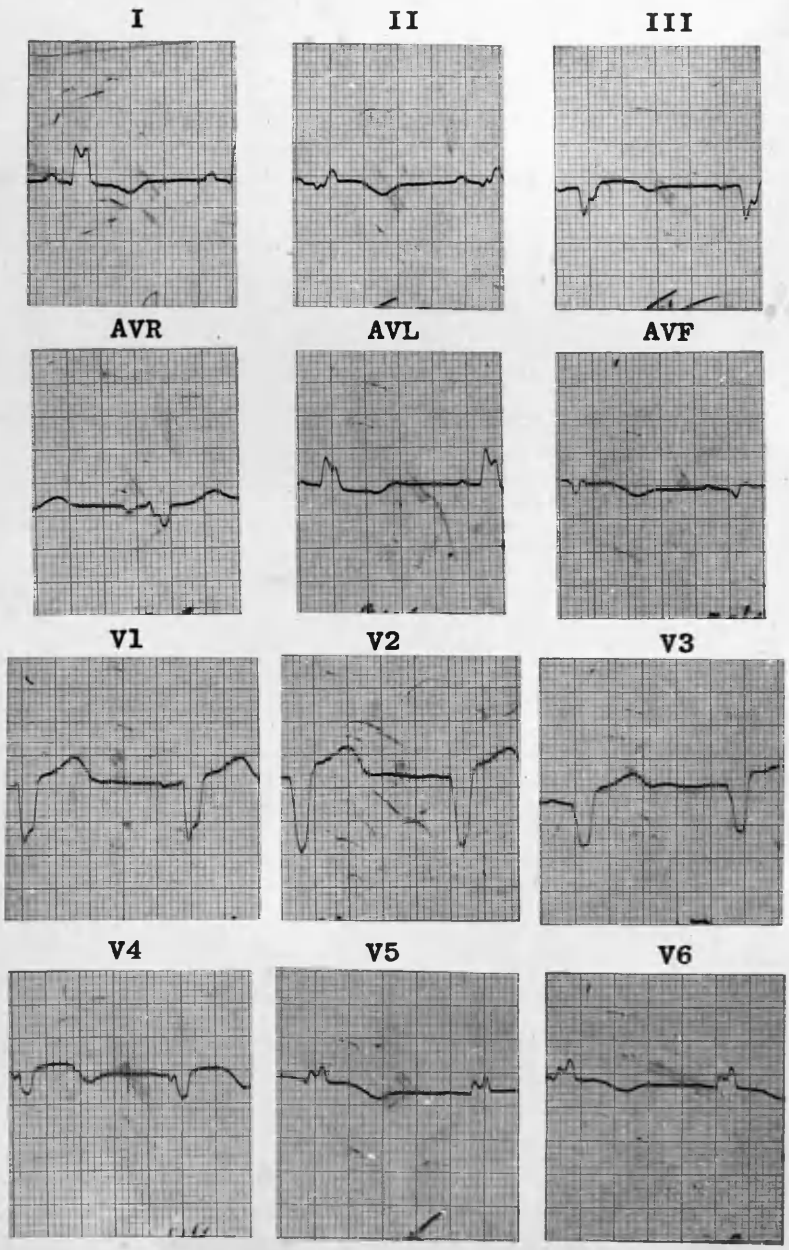


PLATE 4a.

P.C. (Case B13)

(b) On admission (December 1961) fresh infarct made less obvious by bundle branch block.



group with right bundle-branch block were known to be of long standing. The remaining case also in the treated group died on the sixth day with no change in the right bundle-branch block.

If it were possible to reverse bundle-branch block with steroid therapy, this would be a valuable diagnostic aid, since the appearances of infarct may be obscured, particularly by left bundle-branch block, or the appearance of bundle-branch block as a new entity may be the only indication of infarct. This is neatly illustrated by two cases from this study. Case E.1 admitted with complete heart block had in addition a left bundle-branch block. After eight days of steroid therapy, this resolved to leave an acute, transmural antero-septal infarct. (Plate 3 a and b).

Case B.13 admitted with a second myocardial infarction was known to have a left bundle-branch block for eight months. On admission the cardiogram was unaltered from past records and the diagnosis of fresh infarction was substantiated by serum transaminase levels. This was a control case and had no steroids (Plate 4, a, b).

Abnormalities in the QRS, RT and T Components of the E.C.G. representing the infarct pattern, have been followed through serial records every second day to determine whether any difference could be demonstrated between the groups in rate of return towards normality. Two aspects have been examined:-

1) The return of leads to a normal state, e.g. an inverted T becoming upright, as an indication of reduction in size of the area of injury, and
2) The rate of disappearance of the so-called "current of injury" pattern, that is the time taken for the RT segment

to return to the isoelectric time.

If it can be assumed that the area of peri-infarct inflammatory oedema contributes to the E.C.G. changes, the dispersal of this by therapy might produce a stable pattern, indicative of the final infarct size at an earlier date in the recovery period. Since the steroid therapy is continued for only half the period of observation any subsequent deterioration in the cardiogram after withdrawal of therapy would be further evidence of the value of treatment. That the cardiogram would vary from time to time during the healing phase of an infarct was appreciated; that the fluctuation between improvement and deterioration would be so frequent, so variable and so prolonged after the injury, had not been fully appreciated until this study. In reaching a decision on the point at which a stable pattern could be claimed to have been established, the final cardiogram was inspected and then the series of records traced backwards to the earliest point at which that pattern had presented. In calculating an average rate of evolution, those cases who died have been discarded. In one case among the control series, no established pattern had been reached at the end of the 28 day survey; in all others who survived, it was possible to make a decision on a point of stable evolution.

CHAPTER 6.

FEATURES COMPLICATING PROPOSED THERAPY.

1. **Relating to Steroids.**
   - a) Gluco-corticoid effect. - Normal.
     Diabetic.
     Prediabetic.
   - b) Mineralo-corticoid effect - Electrolyte balance.
   - c) Anti-inflammatory action - Beneficial effect.
     Possible effect on healing.
   - d) Hypertension.
   - e) Epilepsy.
   - f) Peptic ulcer.
   - g) Tuberculosis.
   - h) Blood coagulation.

2. **Relating to Dextrose** - rationale for choice.

3. **Relating to Fluid Volume** - Rate of infusion.
   - Effect on mortality in early stages.

Features Complicating Proposed Therapy.

1. Steroids.

a) The gluco-corticoid activity of the administered steroid might be expected to have some effect on carbohydrate metabolism. In the lower dosage used in the trial series, this was thought less likely to be a problem than with the large doses given to the cases of heart block. When subjected to a course of steroid therapy, an apparently normal individual may respond by showing no evidence of carbohydrate upset, by manifesting glycosuria with normal blood sugar levels, or by exhibiting a diabetic type Glucose Tolerance Test. Use has been made of this latter feature in detecting "prediabetic" states (Conn, 1958). In the diabetic individual, often already upset from careful balance by the illness causing admission, the use of gluco-corticoid is likely to disturb the balance still further in favour of hyperglycaemia. The only diabetic to present in this Trial was a mild, elderly diabetic on oral therapy with "Phenformin". While she exhibited some glycosuria and a trace of ketosis on admission, this was not noticeably aggravated during the three days she survived following a severe infarction. The dose of steroid was not modified but 1/6th molar lactate was infused in place of dextrose. This did not aggravate the hyperglycaemia, and compensated for the mild ketosis.

b) Hydrocortisone has more gluco-corticoid activity than mineralo-corticoid, but is not devoid of salt retaining properties, and the possibility of inducing salt and consequently fluid retention in a patient in whom the balance between excretion and intake may be extremely sensitive, caused

considerable concern. But for this, larger doses would have been used in the Trial series. The dose decided upon was based on a compromise between what might be expected to be an effective level, and what might be a harmful dose of mineralo-corticoid with particular reference to the subject in whom heart failure complicated the myocardial infarction. As it transpired, of the 50 cases observed, 18 exhibited sufficient evidence of cardiac embarrassment to be classed as showing signs of "failure" of these 11 died (61%). Among the 100 cases surveyed as a yardstick, "failure" was present in 29 (29%) of whom 20 died (69%). Billings et al (1949) reported that a mortality rate of 52% accompanied either basal rales, or hepatomegaly as complications of acute infarction and Rathe (1942) placed "failure" high among the list of complications contributing to a poor prognosis.

In the present trial, the incidence of "failure" as a feature in the hydrocortisone treated group was 11 cases of 25, an incidence of 44%, of whom 6 died, a mortality rate of 54.5% which is very close to the expected figure. Among the control cases, a rather higher mortality presented in association with failure (71%). This would suggest that the steroid, per se, did not cause any increase in the frequency of failure, or in the mortality expected from this complication. In all cases in which any degree of cardiac embarrassment was detected on the initial examination, diuretic therapy with an intravenous preparation of Chlorothiazide, said to be effective within one hour, was given one hour prior to the institution of the intravenous infusion. Thereafter oral diuretic therapy was used as a routine in such cases, with occasional recourse to an injection of a mercurial diuretic if satisfactory response was not forthcoming.

The use of steroids in the treatment of resistent cardiac oedema is one of the therapeutic paradoxes met with in modern medical practice. One of the cases of heart block had severe cardiac failure with gross hepatomegaly and marked increase in venous pressure, to the extent that the possibility of a haemopericardium, or pericardial effusion was considered (Case E.7). During a second course of steroid therapy initiated because of a sudden collapse, he showed a marked increase in diuresis, and a progressive reduction in the signs of failure.

While the likelihood of aggravating cardiac failure by giving steroids has not been illustrated in this investigation, the beneficial effect of steroids on urinary output in cardiac failure has been observed in one case and this helpful action must be borne in mind in considering the noxious side effects of these potent drugs.

c) The anti-inflammatory action of steroids is the effect sought in the therapeutic use of these drugs in its present context, and is discussed in detail later. Among the other effects of reduction in fibrous tissue formation which must be borne in mind when embarking on treatment, is the prospect of causing acute peptic ulcer, perforation or haematemesis from existing peptic ulcers, or the breakdown of "healed" tuberculous disease. Compared with the long term steroid therapy used in Rheumatoid Arthritis or Bronchial Asthma, the drug is used in a brief course in the present regime, which is unlikely to do harm in the presence of sound healing. One case among a group of patients previously reported (Dall & Buchanan, 1961) had a fatal haematemesis while having both steroids (oral) and anticoagulant therapy. He had no history of dyspepsia and his bleeding could have arisen from an acute steroid ulcer on the gastric mucosa. Suppression of

connective tissue response, and interference with fibrosis has been reported in connection with wound healing (Ragan et al, 1950; Baker & Whitaker, 1950; Creditor et al, 1950), but the possibility of sound healing during steroid therapy has been well established in animal experiments with reference to myocardial infarction (Chapman et al, 1952; Johnson et al, 1953; Opdyke et al, 1953). From this present study there is additional evidence that even after large doses, given in the presence of an extensive infarct, sound healing can occur and no evidence of ventricular aneurysm formation has been detected up to one year after the acute incident.

d) Since hypertension is noted in the previous history of four of the hydrocortisone trial cases, the effect of steroids on blood pressure reported by Perera et al (1950) is of considerable interest. They observed that when given to Normotensive individuals, little or no effect was observed on the blood pressure, whereas when given to those with hypertension, a pressor effect was produced. This was more obvious with D.O.C.A. than other steroids. This report helps to explain a curious effect observed in one of our early cases. The patient (Case A.9) had a blood pressure of 100/85 mm.Hg. on admission. During the course of the hydrocortisone infusion, her blood pressure was recorded at 180/100 mm.Hg. The following day a pressure of 125/80 mm.Hg. was recorded, and subsequently 110/70 mm.Hg. Until the work of Perera (1950) was known no explanation for this isolated reading was forthcoming. Since hypotension, cerebral insufficiency and renal insufficiency are possible serious consequences of myocardial infarction in the formerly hypertensive patient, this side effect of steroids may be of value, rather than a handicap.

e) The same case (Case A.9) illustrated a further complication of steroid therapy. Hydrocortisone has been shown to cause hyper-excitability as observed in Electroencephalogram studies (Woodbury et al, 1950) and to have an effect antagonistic to Phenobarbitone and diphenyl hydantoin in this respect. The patient was an epileptic, subject to petit mal fits for which she took phenobarbitone, grains one, twice daily. On the ninth day of the steroid regime she had a minor seizure. She continued to have several fits per day until the dose of anticonvulsant therapy was built up to phenobarbitone, grains one, three times daily and Mysoline (Primidone, 0.25 gm.) twice daily. No other case exhibited fits as a result of therapy.

f) The possibility of causing activity in peptic ulceration was considered, but it was felt that if buffered prednisolone was used in cases with ulcer history and an antacid regime observed, a sixteen day course of therapy such as was envisaged could be undertaken with only a slight added risk of haematemesis or perforation. No cases at risk occurred in the trial series.

g) A similar problem would have arisen if a known case of recently healed pulmonary tuberculosis had presented with myocardial infarction. In this case, the risk of causing breakdown of scarring in the lung and reactivating the disease would have been considered sufficient to exclude such a patient from the trial, since the value of the proposed steroid regime was not established.

h) Crossgriff et al in two articles (1950 and 1951) has suggested a state of hypercoagulability of the blood during steroid therapy, and observed cases of thrombophlebitis occurring during therapy. In this trial, all

patients had anticoagulant therapy from the outset and it was felt that this would virtually exclude the possibility of this particular complication arising.

2. Dextrose 5% infusion was chosen as the medium in which the hydrocortisone should be given to avoid administration of sodium, again with the risk of inducing cardiac failure by the fluid load, very much a prime consideration. The possibility of a diabetic admission to the trial was appreciated and it was decided to allow the use of 1/6th molar lactate instead of dextrose if hyperglycaemia or ketosis was a complicating factor of the acute myocardial incident, since this would help to compensate the acidosis, but to continue with dextrose infusion of the diabetes were mild, well controlled, and ketosis not a feature. In the one case that did present, described previously in relation to steroids in this context, dextrose could have been given without harm, but as 1/6th molar lactate was instituted on the strength of a trace of acetone in the urine, it was allowed to continue. This case apart there was no complication arising out of the infusion of dextrose as opposed to other fluids.

3. Fluid Volume.

As with all other features of the trial, especially the dose of steroids given and the type of fluid given, it was assumed for purposes of preparing the trial regime that acute left ventricular failure following myocardial infarction must be expected, and any regime should be so planned that it could be applied even in this circumstance. To give 540 ml. fluid over a minimum period of 8 hours and in many cases 12 hours, meant adding to the circulating volume at the rate of from 1 to 0.75 ml. per minute. Even

allowing for a period of hypotension and resultant reduction in renal blood flow, it was felt that in the absence of frank renal disease it would be possible to cope with this volume. As a further assistance to the excretion rate, when signs of left ventricular embarrassment, in particular pulmonary oedema were present, the infusion was delayed for one hour and during this period diuretic therapy was started. Given intravenously chlorothiazide is effective within 30 minutes and promotes maximum diuretic effect in the first hour, thus reducing to a minimum the load on the left ventricle prior to the start of infusion therapy.

If the infusion were to augment the mortality by increasing the degree of left ventricular failure, this would be detected by comparing the early and late mortality of the trial cases with that of the 100 cases surveyed to establish the expected mortality. In the hydrocortisone group (A), of 8 deaths, 6 occurred in the first week (75%); in the control group (B) 5 of the 7 deaths occurred in the first week (71%) and in the survey (Group C) of 32 deaths, 27 (75%) occurred in the first week. The similarity of these figures suggest that the infusion of fluid to a volume of 540 ml. over a period of more than eight hours, did not influence the mortality rate in the trial cases.

Only in one hydrocortisone treated case did any evidence of fluid retention and overloading occur. This was in case (E.5) - among the cases of heart block. Here the circumstances considered in the qualifying remarks on the fluid load applied, in that there was existing renal damage from hypertension. The patient was admitted to hospital some 48 hours after the occurrence of myocardial infarction, and he was hypotensive at that time. There followed a period of severe oliguria, lasting three days

during which time intravenous fluids were used to maintain a more normal electrolyte state. The combined effect of oliguria, continuous intravenous fluids and hydrocortisone (700 mgms on first day) resulted in the appearances of facial oedema, tachycardia, basal crepitations and elevated jugular venous pressure, a state which improved gradually over the next five days as urinary output increased. Except in this case, fluid retention or inability to tolerate the 540 ml. infusion has not been observed.

The results of therapy in the trial cases have justified in one aspect the careful conception of the dose of steroid and the method of administration, in that, apart from a single record of a hypertensive effect, and the promotion of seizures in an epileptic subject, there were no symptoms that could be attributed to the regime, nor has any serious side effect occurred to interrupt therapy.

GROUP C1.

CASES SURVEYED TO ESTABLISH VALIDITY OF CONTROL GROUP

Case	Sex	Age	QS	qR	Shock	Failure	Previous History	Outcome.
J.D.	M	64	+	-	+	+	-	Died 10th day.
J.P.	F	63	+	-	+	-	-	Died 3rd day.
M.G.	F	81	+	-	-	-	-	Home.
A.C.	M	60	+	-	-	-	Angina 3/12	Home.
E.M.	F	63	+	-	-	-	C.A.T.	Died 18th day.
J.U.	M	62	-	+	-	-	-	Home.
W.W.	M	62	+	-	-	-	-	Home.
J.McL.	M	58	+	-	-	-	-	Home.
W.McL.	M	53	+	-	-	-	Hypertension	Home.
W.G.	M	65	+	-	-	-	-	Home.
A.G.	M	46	not known	-	+	+	-	Died 1st day.
D.C.	F	62	+	-	+	-	-	Died 3rd day.
W.E.	M	47	+	-	-	-	-	Home.
J.G.	F	72	not known	-	+	+	-	Died 1st day.
M.McM.	F	67	-	+	-	-	Hypertension	Home.
L.M.	F	69	+	-	+	+	Myocardial infarct.	Died 4th day.
R.R.	M	70	+	-	-	-	-	Home.
F.B.	M	70	+	-	-	-	-	Home.
W.McK.	M	61	+	-	+	+	-	Died 2nd day.
J.P.	F	63	+		+	+	M.S. + A.F.	Died 3rd day.

GROUP CII.

CASES SURVEYED TO ESTABLISH VALIDITY OF CONTROL GROUP.

Case	Sex	Age	QS	qR	Shock	Failure	Previous History	Outcome.
W.S.	M	77		+	-	-	C.A.T. + A.F.	Home.
J.D.	M	64	+	-	+	-	-	Died 11 days.
S.P.	M	70	+	-	+	-	-	Home.
H.J.	F	68	+	-	+	+	-	Died 3rd day.
M.O'N.	M	68	+	-	+	-	Angina 1 yr.	Died 1st day.
S.D.	M	70	+	-	-	-	Angina 3/52	Home (2nd inf. in Hospital).
J.McK.	M	69	+	-	+	+	Angina 2/12	Home.
T.L.	M	64	+	-	+	-	-	Home.
A.F.	F	56	+	-	-	-	High B.P. 18 yrs.	Home.
W.K.	M	45	-	+	-	-	-	Home.
J.C.	M	61	+	-	-	-	-	Home.
A.W.	M	64	-	+	-	-	Myocardial Inf. + ang. 10 yrs.	Home.
T.M.	M	33		+	-	-	-	Home.
J.D.	F	62	+	-	-	-	Myocardial inf. x 2 in 5 yrs.	Home.
L.A.	M	52	-	+	-	-	-	Home.
J.M.	M	68	+ (+ LBBB)	-	+	+	Angina 3 yrs.	Died 1st day.
J.P.	F	56	+	-	-	-	-	Home.
G.F.	M	61	+	-	-	-	Angina 10/12	Home.
J.A.	M	77	+		+	+	-	Died 1st day.
M.C.	M	46	-	+	+	+	Hypertension	Home.

GROUP CIII.

CASES SURVEYED TO ESTABLISH VALIDITY OF CONTROL GROUP.

Case	Sex	Age	QS	qR	Shock	Failure	Previous History	Outcome.
H.L.	M	66	+	-	-	-	-	Home.
E.S.	F	56	+	-	+	-	-	Home.
E.S.	F	66	+		-	-	Angina 3 yrs.	Home.
W.C.	M	51	+		-	-	-	Home.
N.G.	M	53	-	+	+	-	Myocardial inf. x 3.	Home.
E.K.	F	64	+	-	+	-		Home.
J.B.	M	46	+		+	+	Angina + myocardial inf.	Died 3rd day.
D.S.	M	75	+		+	+	-	Died 1st day.
J.W.	M	60	+		-	-	-	Home.
J.H.	F	68	+		+	-	-	Home.
W.B.	M	69	-	+	-	-	Myocardial inf. + Angina	Died 18th day.
S.C.	M	48	+		-	-	-	Home.
W.Y.	M	66	+	-	-	-	-	Home.
C.C.	F	69	+	-	-	-	-	Home.
J.S.	M	51	+		+	-	A. infarct 2 days	Died 2nd day.
H.R.	M	48	-	+	-	-	Myocardial inf. 3 yrs.	Home.
M.G.	F	52	-	+	-	-	Prev. infarct.	Home.
G.P.	M	73	+	-	-	-	-	Home.
W.H.	M	67	+	-	+	-	Angina 6/12	Home.
C.G.	M	61	+	-	-	-	Angina 3/12	Died 10th day.

GROUP CIV.

CASES SURVEYED TO ESTABLISH VALIDITY OF CONTROL GROUP.

Case	Sex	Age	QS	qR	Shock	Failure	Previous History	Outcome
J.McL.	F	54	+	-	+	+	Prev. infarct 1 year.	Died 8th day.
J.H.	M	62	+	-	+	+	Prev. infarct 1/12	Died 1st day.
G.H.	M	60		+	+	+	Angina 6/12	Home.
W.K.	M	75	+	-	+	-	-	Home.
J.M.	M	72	+	-	+	-	-	Home.
W.S.	M	74	+	-	+	+		Died 1st day.
R.T.	M	65	+	-	-	-	-	Died 28th day.
J.M.	M	61	+		-	-	Old Infarct	Home.
T.C.	M	69	-	+	-	-	-	Home.
M.D.(1)	F	64	+	-	-	-	Angina 3 yrs.	Home.
M.D.(2)	F	64	-	+	-	+	Angina + prev. Myocardial Inf.	Home.
J.T.	M	34	+	-	-	-	-	Home.
C.R.	M	52		+	-	-	-	Home.
J.McD.	M	48	+	-	-	-	Angina 2/12	Home.
L.McA.	M	61	+	-	-	-	-	Home.
J.J.	M	47	-	+	-	-	Angina 3/12	Home.
A.B.	M	59	+	-	-	-	Angina 3 yrs.	Home.
M.B.	M	61	+	-	-	-	C.T. 3 yrs.	Home.
E.C.	F	60	not known		+	+	-	Died immediately.
J.D.	M	46	-	+	-	-	Angina 2/52	Died 2nd day.

GROUP CV.

CASES SURVEYED TO ESTABLISH VALIDITY OF CONTROL GROUP.

Case	Sex	Age	QS	qR	Shock	Failure	Previous History	Outcome.
M.McD.	F	62	+	-	++	+	Angina +	Died 2nd day.
J.P.	F	47	not known	PR	++	-	-	Died 2nd day.
K.McS.	F	46	-	+	-	-	-	Home.
H.J.	F	68	+	-	+	+	Angina 2/12	Died 3rd day.
C.P.	M	70	+	-	-	-	Angina.	Home.
F.C.	M	74	+	-	-	+	Angina 5/52	Died 14th day.
G.R.	F	69	+	-	-	+	Angina 6/52.	Died 3rd day.
A.W.	M	72	+	-	+	-	-	Home.
J.D.	M	66	-	+		+	Angina 10	Home.
C.McG.	F	73	-	+	-	-	Angina 1/12	Home.
J.S.	F	74	+	-	+	+	Angina 6 yrs.	Died 6th day.
M.McC.	F	79	+	-	+	+	Angina.	Died 7th day.
C.McI.	F	76	+	-	-	+	-	Home.
J.C.	M	54	+	-	-	-	-	Home.
T.McM.	M	71	+	-	+	+	-	Home.
M.B.	F	77		+	+	-	-	Home.
C.W.	F	62	-	+	+	-	Angina years.	Home.
J.D.	M	66	+	-	-	+	-	Home.
W.C.	M	58	+		+	+	Infarct +	Died 1st day.
M.E.	F	85	+		-	+	Angina 10 yrs.	Died 10th day.

CHAPTER 7.

METHOD OF GRADING THE SEVERITY OF INFARCTION.

BASED ON FEATURES EXHIBITED IN 100 CASES OF ACUTE INFARCT.

1. Clinical Features.

A) Shock.

B) Failure - Left heart failure.

- Right heart failure.

C) Previous history of cardiovascular disease - Hypertension.

- Rheumatic heart disease.

- Coronary Artery disease.

2. Electrocardiographic Features.

Major infarction.

Minor infarction.

3. Application of grading to show mortality rate corresponding to severity of grading.

Method of Grading the Severity of Infarction.

It was assumed that in a small trial, even with random sampling of cases, it was unlikely that there would be an even distribution of severe and mild cases between the groups. For this reason, a method of grading the cases into severe, moderately severe, average and mild infarcts was drawn up so that the distribution of the cases could be compared as well as the mortality rates. To do this a combination of clinical and electrocardio-:graphic features has been used.

In the consideration of overall prognosis, and the features of significance, the work of Woods and Barnes (1942), Master et al (1942), Wooten and Kyser (1953) and Jacobs (1957) has been of assistance. The ingenious but complex Pathological index of Schnur (1953(a) and (b)) illustrated the value of a common assessment scheme, but also the error of a detailed and complicated system. Current work being undertaken (Peel et al, 1962) has shown the possibility of applying a points scoring system (Coronary Prognostic Index) to myocardial infarct cases by which the patient may be placed into one of several categories according to the clinical and E.C.G. features on admission. This has been of the utmost value and stresses the importance of a simple regime. As this work is not yet available for reference, the scoring system has not been used but the findings have influenced the clinical features on which the grading of cases as severe, average and mild is based.

As severity of the injury was being assessed, it is logical that the features seen in severe cases should be utilised in this grading so that presence of these features will weight a case towards the severe categories

TABLE 4.

THE EFFECT OF SHOCK ALONE (MILD) AND SHOCK AND FAILURE (SEVERE) ON SURVIVAL (GROUP C).

GROUP C.

	Shock alone	Shock with failure	Failure alone
Total	18	23	29
Alive	12	4	8
Mortality	33%	82.7%	72.5%

and absence of these features will occur in the mild cases of infarct. These features were assessed as recorded at the time of admission to hospital.

1. Clinical Features.

A) The occurrence of shock is well recognised as an indication of a myocardial injury of some gravity (Billings et al, 1949; Bean & Read, 1942; Epstein & Relman, 1949). That the clinical picture of shock may range from a patient who is cold, clammy and apprehensive to another who is prostrate, with absent peripheral pulses, inaudible heart sounds and peripheral circulatory failure was appreciated, and in taking this range together as one feature without any extra-weighting for degrees of shock, allowance was made for the fact that those exhibiting severe degrees of shock would manifest some indication of cardiac failure whereas those with mild shock were less likely to do so, and a separation of these cases would occur in this way. This was borne out by the analysis of the 100 cases surveyed (Group C). Where shock occurred alone a mortality of 33% resulted but where shock and failure occurred together, as in the cases with severe shock, a mortality of 82.7% is seen (Table 4). Peripheral circulatory failure, tachycardia with a pulse pressure of less than 30 mm.Hg. a cold sweat, and pallor were taken as features indicating shock.

B) Failure was considered to be present when there was evidence of cardiac embarrassment, either as crepitations at the bases of the lungs, orthopnoea or pulmonary oedema; or raised venous pressure, hepatomegaly or oedema. The features of left ventricular decompensation can readily be appreciated as arising from acute infarction. Those of congestive cardiac failure may seem not so closely linked with a recent injury as to

TABLE 5.

THE EFFECT OF INDIVIDUAL FEATURES ON SURVIVAL.

GROUP C.

	All Shock	Prev. History	Failure
Total	41	47	29
Alive	16	27	8
Mortality	61%	42.5%	72.5%

be included in the same category, but it was considered that the presence of oedema, or congestive cardiac failure either coincident with or prior to the myocardial infarction would indicate a heart already incapacitated by other factors. In some reported series congestive cardiac failure occurs in as many as 48% of infarcts (Chambers, 1946) and combined right and left heart failure may result from an infarct affecting mainly the left ventricular wall (White & McGinn, 1933; Master et al, 1937). It has been suggested that where a large area of the interventricular septum is damaged, rapid engorgement of liver and distension of the neck veins results (Fishberg et al, 1934; Master et al, 1937) presumably as a result of a Bernheim type of effect, with bulging of the damaged septum into the cavity of the right ventricle, during the powerful systolic contraction of the other ventricle. No attempt was made to assess degrees of "failure" since the mortality in those with "failure" of any description was 72.5% and of all the individual features "failure" had the highest mortality rate (Table 5).

C) Previous History. In considering this point it was reasoned that a history of hypertension, or rheumatic heart disease, while not so directly involved with infarction as a history of coronary artery disease, did mean a heart that was less able than normal to cope with an acute injury. It might be argued that such a heart would more readily fail, and a weighting would be achieved in this manner, but although this was so in the one case of rheumatic heart disease in the group (Case 20, Group C) in the four cases with a history of hypertension, only one showed "failure" as a feature. In the absence of evidence that failure was a likely feature of these

TABLE 6.

EFFECT OF PREVIOUS HISTORY ON SURVIVAL.

GROUP C.

No.	Angina Only	Infarct Only	Coronary Artery Disease	Others
Total	25	17	42	5
Survivors	14	9	23	4
Mortality	44%	47%	45.2%	20%

TABLE 7.

INFLUENCE OF TYPE OF INFARCT ON SURVIVAL.

GROUP C.

	Major Infarct	Minor Infarct
Total	74	22
Survivors	45	20
Mortality	39%	9%

cases, it was necessary to award a weighting factor for a previous history of these forms of cardiovascular disease. Reference was made to the collected statistics of Doscher and Poindexter (1950).

No distinction was drawn between a previous history of infarction and a history of angina for the following reason. The mortality rate for the whole group with a significant past history was 42.5% (Table for coronary artery disease as a whole, a mortality of 45.2% occurred and as both angina and infarcts considered separately did not differ by more than 2% from this figure (see Table 6), there was no useful point to be gained in subdividing two so closely similar categories.

2. Cardiographic Features (Group C).

While no case of infarct is without risk, it is generally accepted that those with minor changes in the cardiogram are less dangerous and have a better prognosis (Papp and Smith, 1955; Plotz, 1957) and for this reason a differential weighting was preferred for this factor.
Where a "major" infarct had occurred, with consequent changes in the QRS component of the tracing, a mortality rate of 39.2% was observed in a total of 74 cases. In 22 cases showing a qR or RT alteration (a "minor infarct"), a mortality of 9% occurred (Table 7). Four cases died without cardiographic records. Since the mortality of the major infarcts was in excess of the overall mortality (34%) for all cases and all factors, it was decided to allow a weighting for major infarcts, but to neglect minor infarct changes since these did not appear to influence the mortality.

3. Age and Sex.

The influence of age and sex on the prognosis has been considered by

TABLE 8.

RELATION BETWEEN FEATURES EXHIBITED AND MORTALITY

FEATURES.

GROUP C.

No.	All 4	Any 3	Any 2	1 only or less.
Total	12	15	32	37
Deaths	11	11	5	3
Mortality %	91.5%	73%	15.6%	8%
GRADE	SEVERE	MOD. SEVERE	AVERAGE	MILD
DISTRIBUTION	29.1%		31.3%	39.5% of total.

Mintz and Katz (1942), Baer and Frankel (1944), Sigler (1951), Barr (1955) and Peel (1955) and it was recognised that there is a considerable difference in outlook for a 40 year old and a 70 year old with a similar infarct, but it was intended to keep the system of grading as simple as possible, and confined to the features more closely linked with the severity of myocardial injury. It was felt that shock, failure and a previous history would be more common with advancing years and in this way would add sufficiently to the weighting without further consideration.

Use of Features in Grading.

As described, it has been determined that shock, failure, a previous history of cardiovascular disease and evidence of a major infarct should be considered as significant in assessing the severity of any infarct.

Using these features the cases could be divided into severe, moderately severe, average or mild according to whether they exhibited 4, 3, 2, 1 or none of the features considered. Applied to the 100 cases of Group C, this method of grading showed a differential mortality expectancy in keeping with the degrees of severity (Table 8) ranging from 91.5% when all four features were present to 8% when only one or less (e.g. qR infarct) could be scored. Those whose E.C.G. features were not known because of early death had a score of 2 or more without E.C.G. features. Although it is likely that a major infarct occurred, it is not sufficiently certain to allow a weighting of all four deaths as a major infarct, so in assessing mortality of the groups these four cases have been discarded as information is incomplete. It will be observed that of the 100 cases examined, a very even scatter of cases has been obtained, thus making it an excellent base line against which to observe the trial results and the distribution of cases.

CHAPTER 8.

MATERIAL ANALYSIS AND RESULTS.

1. Cases of Heart Block:
   - (i) Chronic Heart Block.
   - (ii) Group on oral therapy.
     rhythm change.
   - (iii) Group on I.V. therapy.
     rhythm change.
   - (iv) Cases with long standing block.
     - possible differing mode of action.
   - (v) Fate of the Untreated Case.

2. Bundle-Branch Block.

3. Arrhythmias.

4. Trial Cases.
   - (i) Effect of Severity on mortality.
     Sex.
     Age.
     Shock.
     Failure.
     History.
   - (ii) Distribution of cases.
   - (iii) Expected mortality.

TABLE 9.

INCIDENCE OF COMPLETE HEART BLOCK.

	Complete Heart Block	Cases Reviewed	Percentage
Kerr 1937 (collected cases).	17	1,124	1.5
Master et al 1938.	6	375	1.6
Rosenbaum & Levine 1941.	5	208	2.4
Condry & Thompson, 1957.	14	425	3.3
	42	2,132	2%

GROUP D.

A.F. (65)	PREVIOUS INFARCT (1956)	COMPLETE BLOCK.	FRESH POST-:ERIOR INFARCT	PREDNISOLONE 4	SINUS RHYTHM IN 36 HOURS.	REMAINS WELL. NO THERAPY 9 MONTHS.
M.F. (59)	NIL	A.V. DIS-ASSOCIATION	ANTERIOR AND POSTERIOR INFARCT	PREDNISOLONE (AFTER 3 DAYS)	SINUS RHYTHM ON 8th. DAY	WELL. ON A/C THERAPY.
R.T. (65)	NIL	COMPLETE WITH A.F.	FRESH POST-:ERIOR INFARCT	DEXAMETHASONE 2 mgm. q.i.d.	WENCKEBACH IN 24 HRS. 1ST. DEGREE 5 DAYS. S.R. < 1 WK.	
J.T. (73)	NIL	COMPLETE BLOCK	FRESH POST-:ERIOR INFARCT	PREDNISOLONE 20mg/DAY	1ST. DEGREE 72 HRS. SINUS RHYTHM	WELL 3/12 NO THERAPY.
A.H. (61)	COR. PULMONALE VENT-TACHYCARDIA	COMPLETE BLOCK	FRESH ANT. INFARCT.	DEXAMETHASONE 2 mg. q.i.d.	S.R. IN 4½ DAYS	DEVELOPED WENCKEBACH WHEN STEROID REDUCED DIED SUDDENLY.
J.A. (63)	NIL	COMPLETE BLOCK	FRESH A/LAT. INFARCT.	I.V. HYDRO-CORT. (100mg) DEXAMETHASONE 2 mgm. q.i.d.	DIED	AUTOPSY - SEPTUM COMPLETELY INFARCTED.
N.U. (63)		COMPLETE BLOCK	FRESH POST. INFARCT.	PREDNISOLONE 5 mgm. q.i.d.	1ST DEGREE 3 DAYS S.R. IN 7 DAYS.	DIED OF G.I. HAEMORRHAGE ? D. U.

GROUP E.

	HISTORY.	CONDUCTION DEFECT.	INFARCT.	HYDRO-CORTISONE THERAPY.	EFFECT.	RESULT.
1.J.S.	Nil	Complete + L BBB.	Acute A/S.	I.V. 650mgms.	Sinus Rhythm	Well 12/12.
2.D.A.	Nil	Complete.	Acute PMI.	I.V. 450mgms.	Sinus Rhythm.	Well 10/12.
3.J.S.	Old Septal infarct	Complete.	Recent Anterior.	I.V. 300mgms.	Nil.	Died 12 Hrs.
4.A.M.	Nil	Complete + R BBB.	Acute A/S.	I.V. 600mgms.	Sinus Rhythm.	Well 6/12.
5.J.M.	Old Ant. infarct	Complete.	Acute PMI.	I.V. 700mgms.	Sinus Rhythm.	Died 10th day.
6.A.W.	Old A/S infarct	Complete after Cardiac arrest.	Fresh PMI.	I.V. 400mgms.	Sinus Rhythm.	Well 4/12.
7.J.F.	Nil	Complete + 3/2 Block.	Acute PMI.	I.V. 300mgms.	Sinus Rhythm.	Well 2/12.
8.R.K.	Nil	Complete	Acute PMI.	I.V. 500mgms.	Sinus Rhythm.	Well 2/12.
9.D.M.	Nil	Complete + R BBB.	Acute PMI.	I.V. 300mgms.	Sinus Rhythm.	Well 4/52.

Group F.

	Age	Sex	Disease	Type of Block	Therapy	Effect.
1.A.T.	83	F	Aortic Stenosis	Complete	Prednisolone 30mgms-48 hrs	Nil.
2.J H.	47	M	Aortic Stenosis (congenital)	Complete	I.V. Hydro-cortisone 100mgms-12hrs	Nil
3.E.S.	49	F	Myocardial ischaemia	Latent P.R.-0.28sec S.A.attacks.	Prednisolone 30mgms/day for 2/12.	P.R.-0.24sec No S.A.attack
4.J.Y.	64	M	Old Infarct.	Latent.	Prednisolone 30mgms/day for 2 weeks	Nil.
5.E.Y.	63	M	Old infarct.	Latent.	Prednisolone 30mgms/day for 2 weeks	Nil.
6.A.C.	71	M	Coronary insufficiency	Complete + Aur. Fib. S.A.attacks	Prednisolone 30mgms/day to maintenance 5 mgms/day.	Vent.rate to 100/min. No S.A.attack

GROUP G.

	Age	Sex	Disease	Type of block	Therapy	Effect
1. A.B.	49	M	Myocardial infarct.	Complete	Ephedrine Hcl.	Sinus Rhythm after 16 days
2. J.S.	76	M	Myocardial infarct.	Varying 3/2 and complete	Nil.	Died 36 hrs.

MATERIAL.

1. Cases of Heart Block.

Complete heart block is reported to occur in about 2% of all cases of myocardial infarction (Table 9). In just over three years, 18 cases of heart block associated with myocardial infarct have been seen at this hospital; of these, five were gravely ill and but for electrocardiogram taken on admission, had any of these died, the arrhythmia would have been undiagnosed. As there is a mortality rate of 45% (Table 2) where the diagnosis is established, and most of the deaths occur soon after the onset of the arrhythmia, it is possible that this complication exists in some of the "fatal" infarcts who do not reach hospital.

1. Heart Block.

Twenty five patients with some degree of heart block have been studied. This consists of 4 cases of latent block (3 in group F and 1 in group A), 18 cases of complete block (Group D, 7 cases; Group E, 9 cases; Group G, 2 cases) of acute onset, and 3 cases of long established complete block (Group F).

(A) Chronic (longstanding) block.

Six cases fall into this category and are detailed in Group F. Three were in latent heart block, arising from coronary artery disease, and all were treated with prednisolone in a dose of up to 30 mgms per day. In two, no effect was apparent. In the third, the only female, the P-R interval was shortened from 0.28 to 0.24 secs. during therapy and increased again on stopping (Case F.3).

Three were in complete heart block; one due to coronary artery disease, one elderly arteriosclerotic female; and one due to congenital

aortic stenosis.

Stokes-Adams attacks were frequent in two cases (F.3; F.6). Treatment resulted in ability to resume employment confidently as Stokes-Adams attacks were very infrequent. Case F.3 had been regarded as an "epileptic" on account of her "fits". If this were true, prednisolone would have increased the number and frequency of fits (Woodbury, 1950); in fact, the fits stopped after steroid was started. In the light of subsequent work published by Pay & Earl Waverley (1961) the daily dose for these patients was low (30 mgm. compared with 80 mgm. per day) and the trial of therapy very short in two of the cases (F.1 and F.2). In case F.6 auricular fibrillation and heart block resulted in frequent Stokes-Adams attacks with a ventricular rate of 40 per minute. No further Stokes-Adams attacks occurred after 24 hours of prednisolone therapy. The ventricular rate rose slowly to 100 per minute, auricular fibrillation when on 30 mgm. prednisolone daily. Gradual reduction of the dose had no effect on rate until 10 mgm. per day was reached. At this level, ventricular rate dropped to 56 per minute. No Stokes-Adams attacks occurred and this has been kept as a maintenance dose.

(B). Acute Heart Block - Oral Therapy.

Seven cases were treated with oral prednisolone or dexamethasone. These were all cases of complete heart block related to acute myocardial infarction. In five, the therapy was with steroids from the outset, and four of these showed reversion to sinus rhythm in $4\frac{1}{2}$ to 7 days. One case died within 12 hours without altering rhythm. It may be considered that therapy had no chance to take effect in this case. In the remaining two cases 4 (D.1) and 3 (D.2) days elapsed between onset of block and start of steroids,

during which time ephedrine was given in full doses. After the start of prednisolone, sinus rhythm was restored in 36 hours and 5 days respectively. In all cases, Stokes-Adams attacks where present, ceased within 24 hours of starting treatment. Case D.5 showed a recurrence of block (Wenckebach Type A) on the day steroids were withdrawn and died the same day.

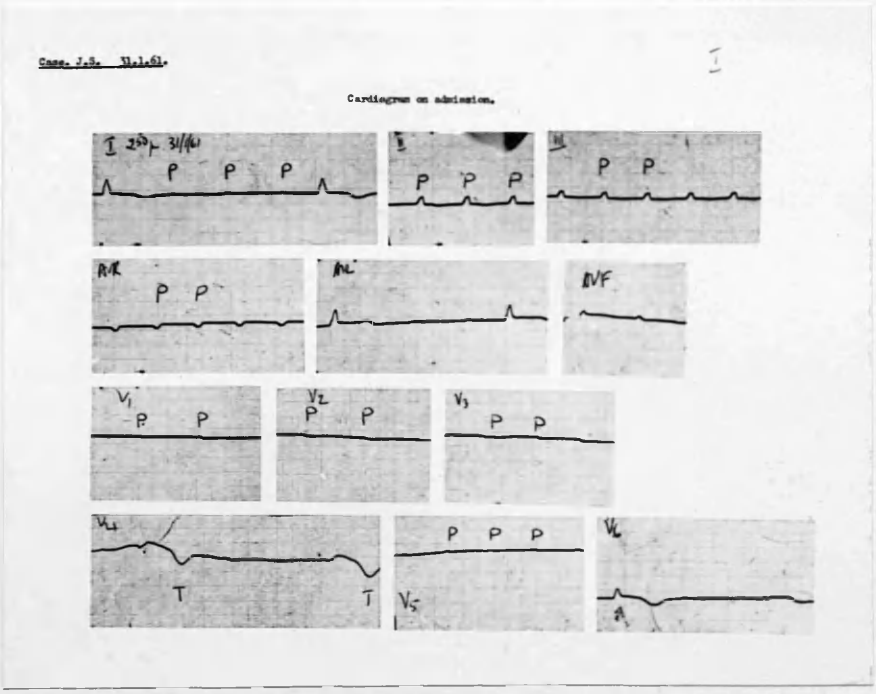
One case (D.6) died of a massive gastro-intestinal haemorrhage. There was no history of dyspepsia, and although on anticoagulant therapy, the prothrombin time was well within the therapeutic range. It may be postulated that this was an acute steroid ulcer which bled. Post-mortem permission was not granted.

The cases in this group recovered sinus rhythm within one week of therapy, ranging from the 5th to the 8th day after infarction. The mortality of 43% (3 of 7 cases) is almost identical with the expected mortality from acute heart block (Table 2). Penton et al (1956), Condry and Thomson (1957) and Gilchrist (1958) have shown that for those cases who survived the acute stage, the prognosis is good, and recovery of sinus rhythm may be expected during the second week (6th - 14th day). It was felt that the time taken to respond to treatment in this group of cases, and the mortality rate, was too similar to the "untreated" results to draw any conclusion as to the value of oral steroid therapy.

(C). Acute Heart Block - Intravenous Therapy (Group E).

During the progress of the study with oral therapy, a case was admitted, gravely ill, and having noted the death of one case before oral therapy could be of value (Case D.6) this patient was given intravenous hydrocortisone, 100 mgm. The effect was dramatic. A moribund patient with a pulse rate of 14 per minute, frequent Stokes-Adams attacks, and Cheyne-Stokes respiration,

RESOLUTION OF COMPLETE HEART BLOCK FOLLOWING ACUTE INFARCTION.



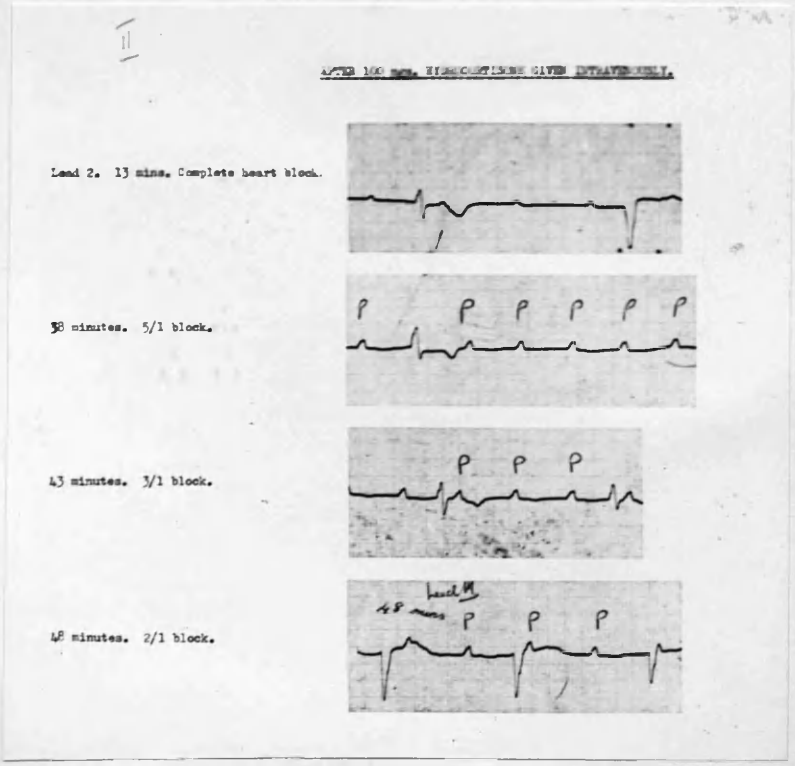
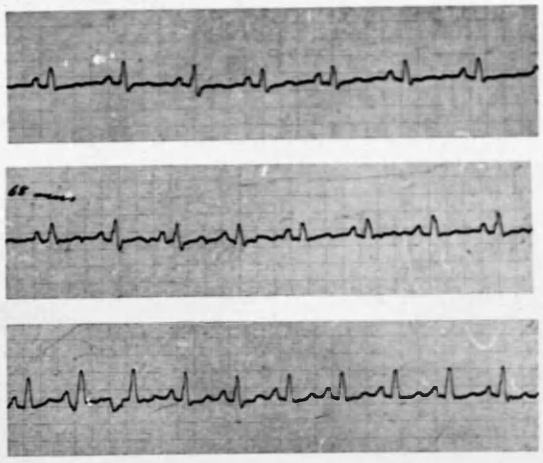


PLATE 5a.

RESOLUTION OF COMPLETE HEART BLOCK FOLLOWING ACUTE INFARCTION.

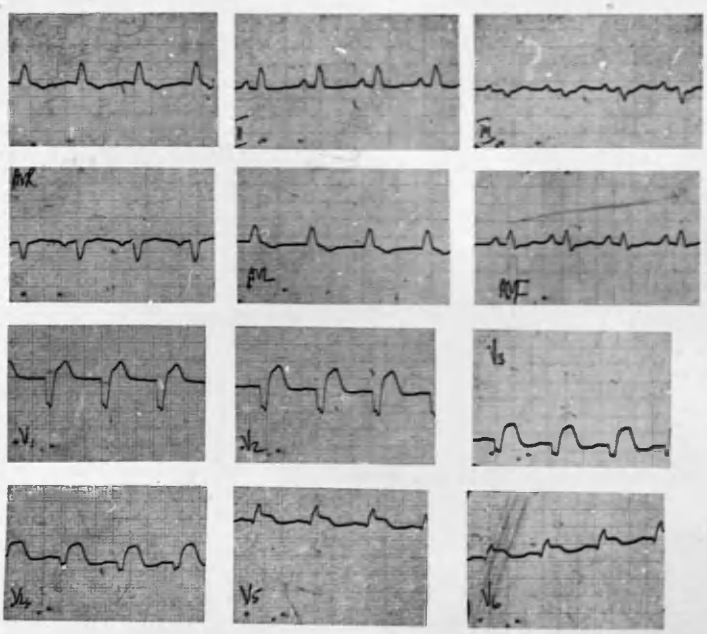
Case. J.S.



Note. Sinus rhythm restored 53 minutes after 100 mgms. Hydrocortisone given I.V.

Case. J.S. 31.1.60

12 Lead E.C.G.

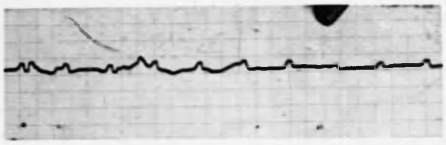


113 minutes after 100 mgms. Hydrocortisone. Sinus rhythm with Left Bundle branch Block and extensive Antero - septal infarction.

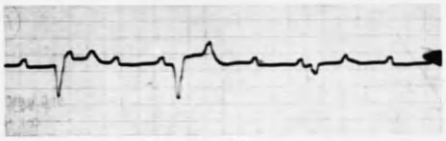
RESOLUTION OF COMPLETE HEART BLOCK FOLLOWING ACUTE INFARCTION.

8. pm. Sinus rhythm.
Drip discontinued.

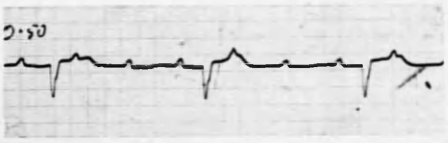
10.30 pm. Varying block.
With Stokes - Adams attacks.



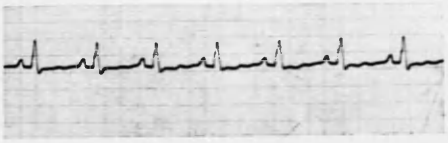
10.35 pm. 100 mgs. Hydrocortisone.
Drip restarted.



10.50 pm. 3/1 Block.



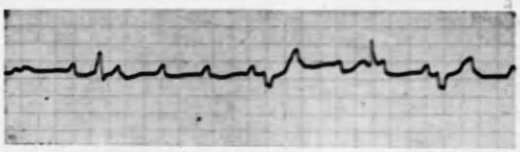
11.10 pm. Sinus rhythm restored.



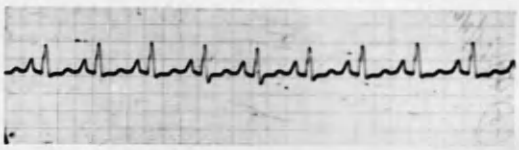
Case J.S. 1.2.61.

V1

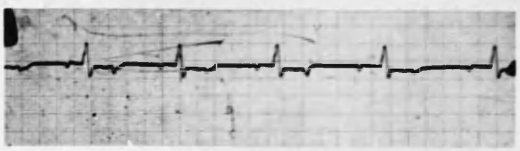
2.45 am. Drip slowed.
Varying block.



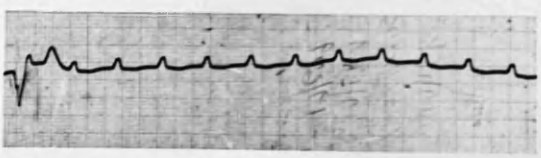
3.0. am. Sinus rhythm restored.



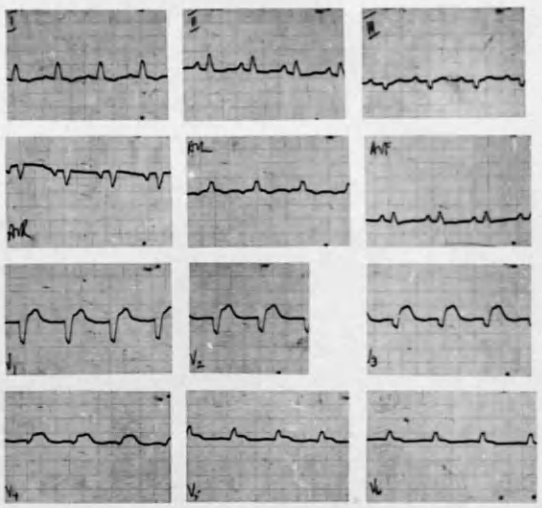
6.0. am. Drip slowed.
2/1 Block.



8.30. am. Stokes - Adams attacks.
Complete block.



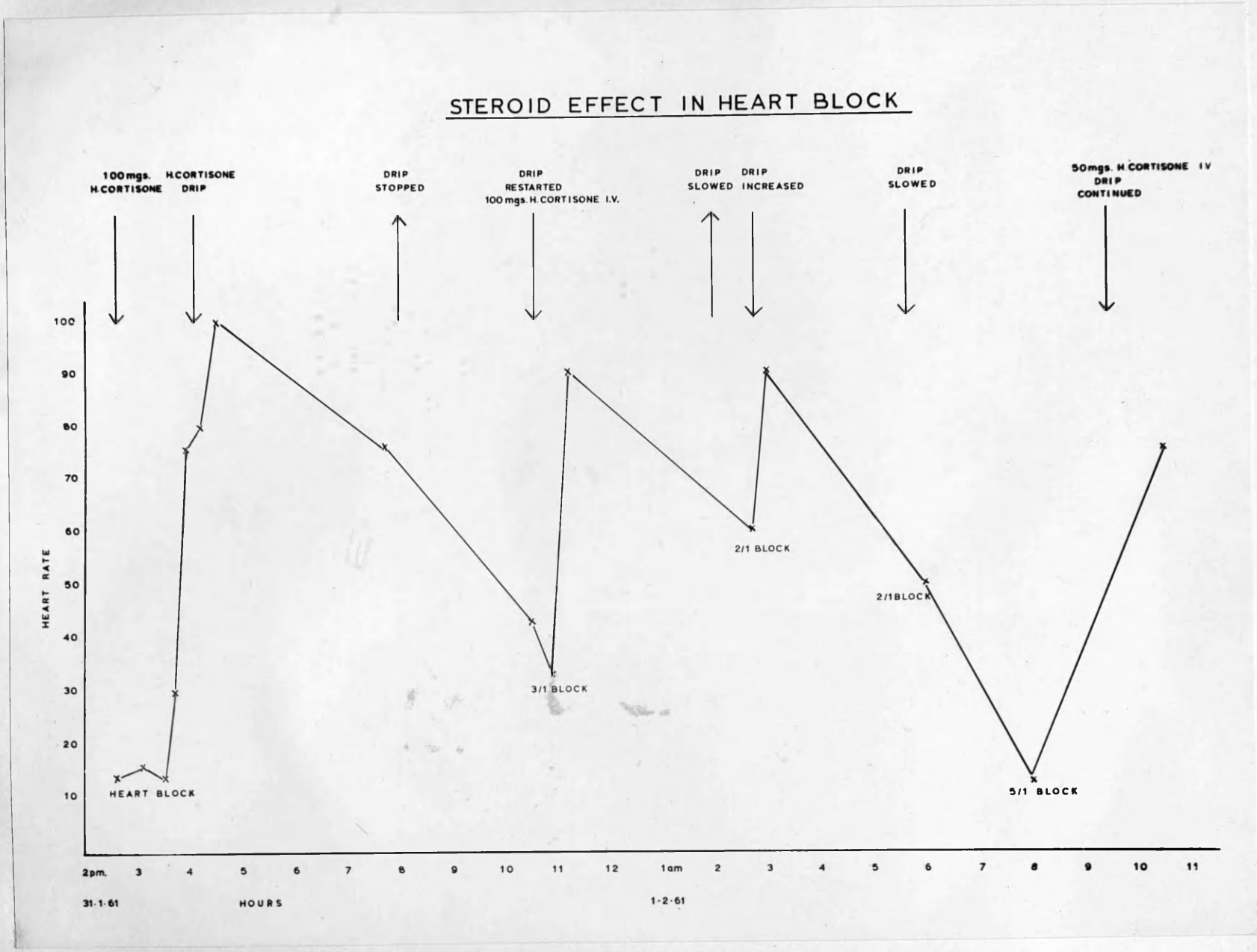
RESOLUTION OF COMPLETE HEART BLOCK FOLLOWING ACUTE INFARCTION.

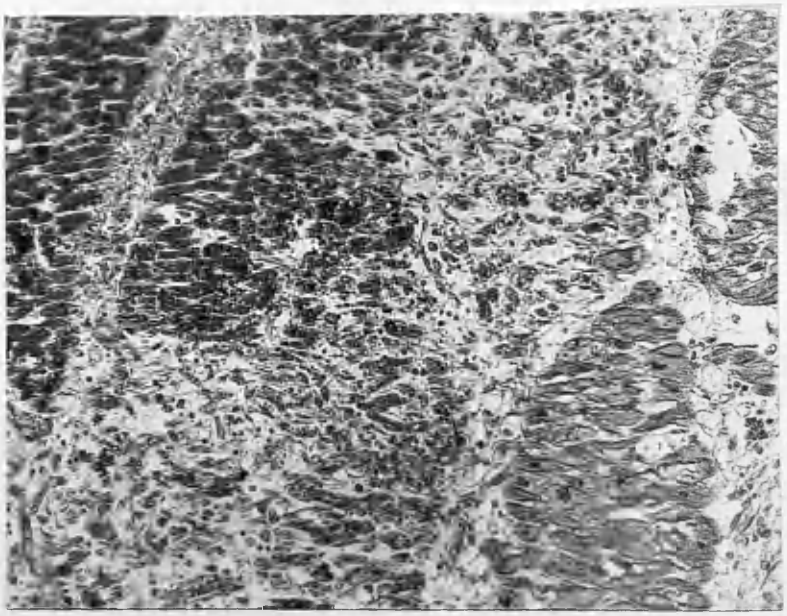


50 mgm. Hydrocortisone given I.V. at 9.30 am.

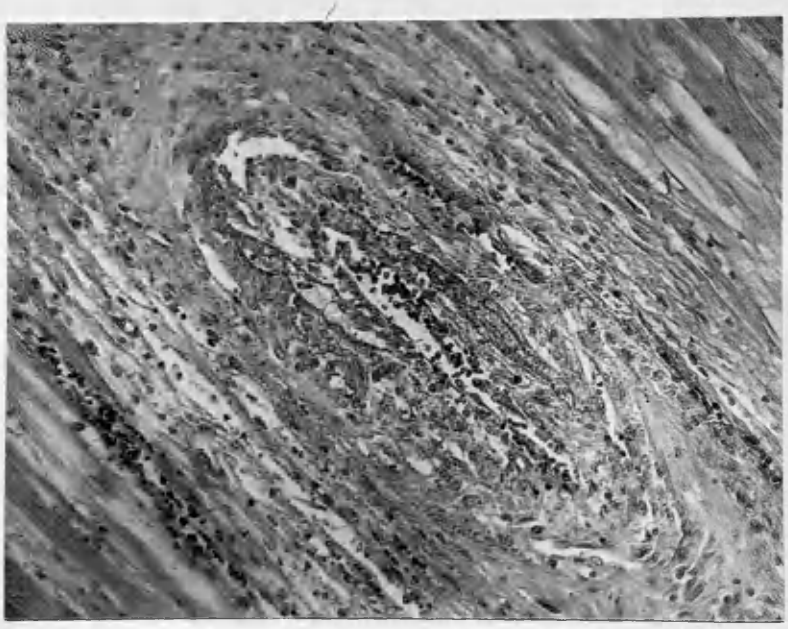
10.30 am. Sinus rhythm with Left Bundle Branch Block and Antero - Septal infarct.

J.S. (Case El.) PLATE 5d.





Area of septum showing old injury with fibrosis in apposition to recently injured muscle. (Top left) Trichrome. X200.



High power view of septum showing organisation and a vessel recanalising.

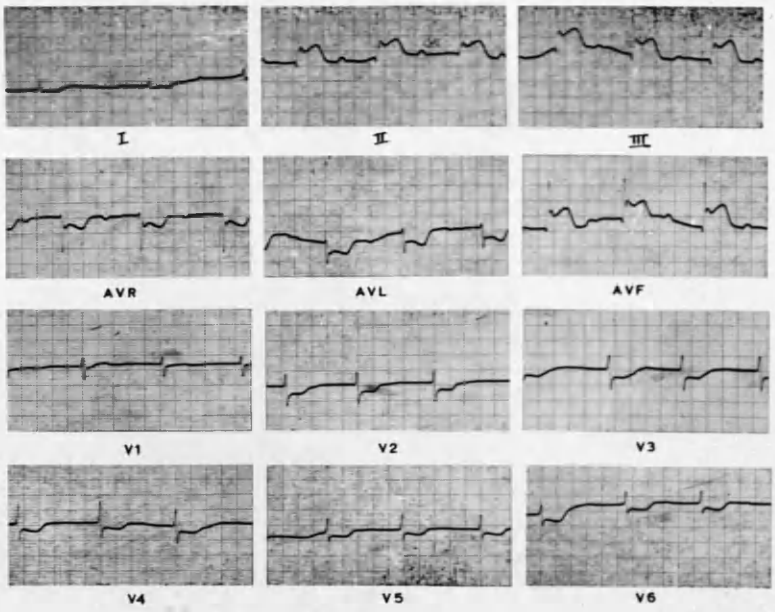
was seen to improve steadily within a matter of minutes. The cardiogram showed complete block, 5 to 1 block, 3 to 1, 2 to 1, a period of latent block, and then sinus rhythm all within 53 minutes of the initial injection (Plate 5). No other therapy was given. The blood pressure was restored, and respiration became normal. To maintain the steroid effect, 100 mgms. of hydrocortisone was put into 5% dextrose solution (540 ml.) and a slow intravenous infusion started. 4 hours later the infusion of dextrose and hydrocortisone was discontinued as the patient was very well and in sinus rhythm. Three hours after this the block recurred. On this occasion sinus rhythm was restored inside 44 minutes by injection of further hydrocortisone injected intravenously. The infusion was slowed for fear of fluid overloading, on two occasions during the following eight hours. On each occasion, this step was followed by recurrence of block which yielded quickly to a further booster dose of hydrocortisone (Plate 5C). In all, 650 mgms of hydrocortisone were given intravenously in 24 hours. There was no evidence of cardiac failure; a mild euphoria was noted at this stage. The routine course of prednisolone was given thereafter.

Of the other eight cases in this group (Group E) seven returned to sinus rhythm within the first 24 hours of therapy. One remained in block and died. In this case, death was due to an extensive anterior infarct (fresh) while the heart block was related to a former posterior infarct and not of recent origin (Case E.3 - Plate 6). In four cases, the sequence of decreasing block noted in case E.1 was recorded at some point during recovery of normal conduction.

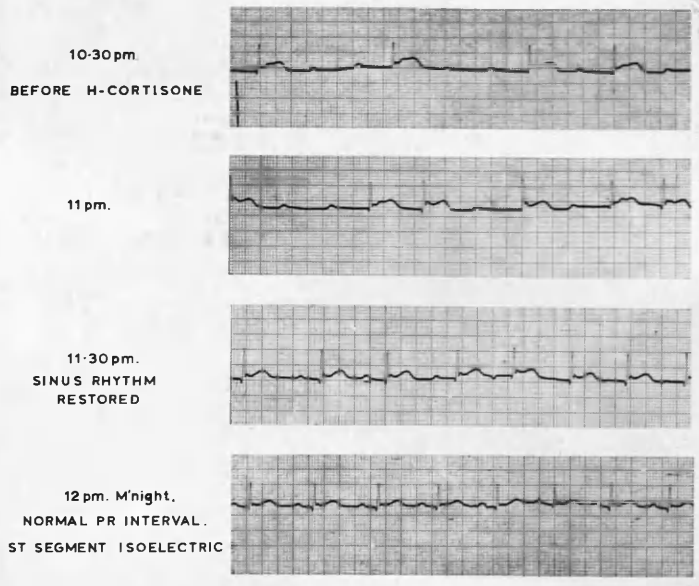
Case E.2 besides illustrating the stages of recovery, showed an additional feature of interest. The initial cardiogram showed an acute injury pattern in the posterior leads, with marked R.T. elevation. During

RESOLUTION OF INFARCT PATTERN AND HEART BLOCK DURING STEROID THERAPY.

CASE D.A. 25-4-61 ON ADMISSION 10-15pm.



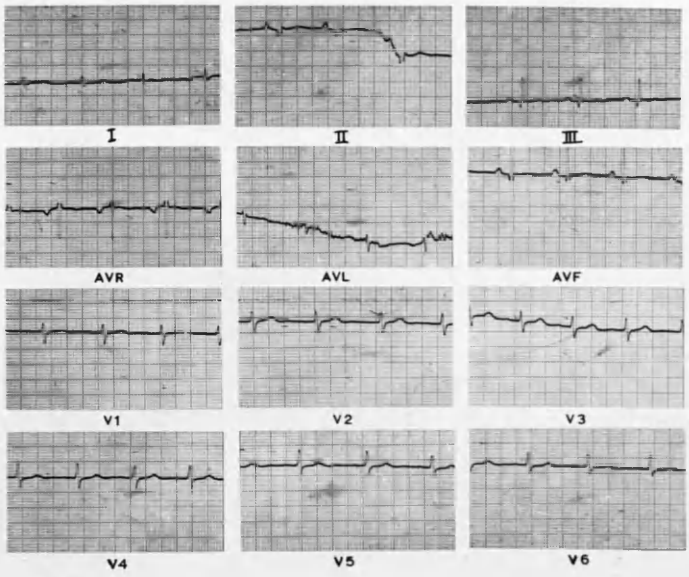
CASE D.A. 25-4-61 AFTER HYDROCORTISONE.



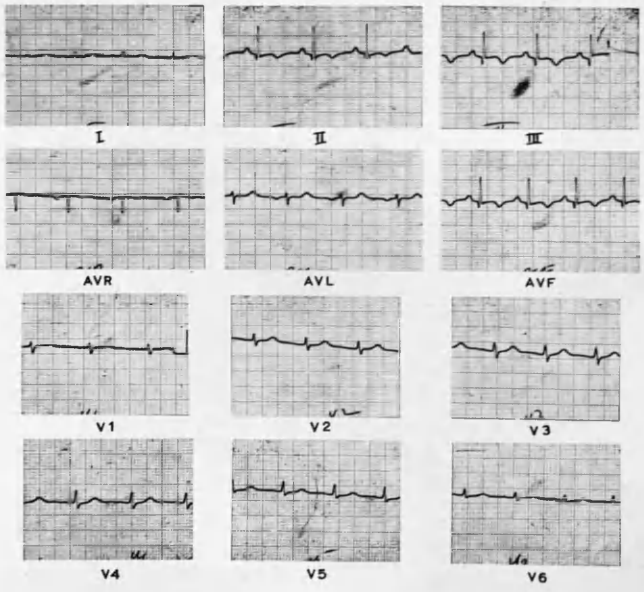
SERIAL RECORDS LEAD II

RESOLUTION OF INFARCT PATTERN AND HEART BLOCK DURING STEROID THERAPY.

CASE D.A. 26·4·61 12 HOURS AFTER HYDROCORTISONE



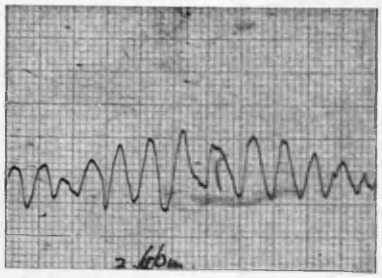
CASE D.A. 27·4·61 AFTER 24 HOURS PREDNISOLONE.



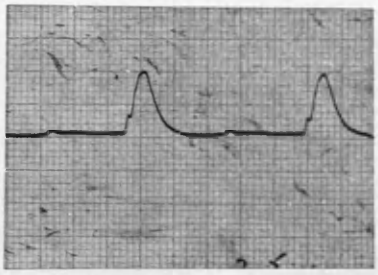
A.W. (Case E.6.)

PLATE 8.

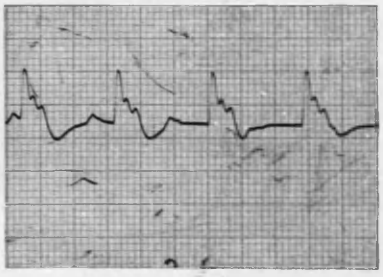
Ventricular Fibrillation. (a)
Hydrocortisone 100 m.gms.
given I.V.prior to defibrillation.



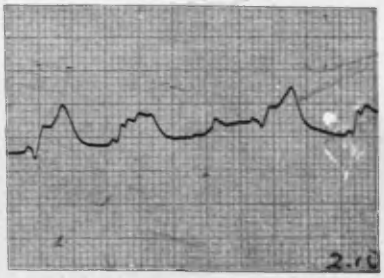
P.R. 0.48 sec.
5 mins. after defibrillation. (b)



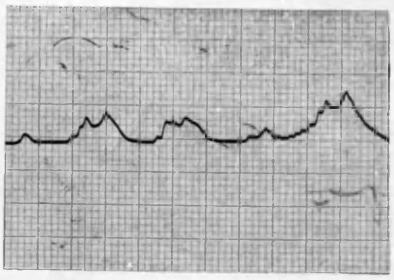
Complete heart block.
6 mins. after shock. (c)



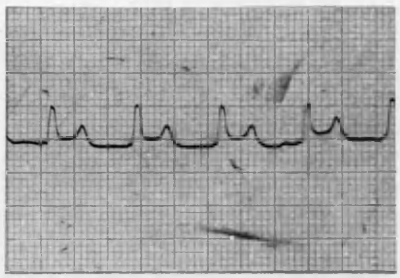
P.R. now 0.28 sec.
10 mins. after shock. (d)



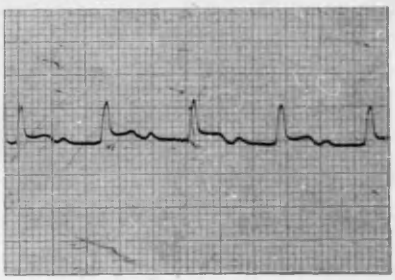
Prior to second injection of Hydrocortisone - disorganised complexes again present. (e)



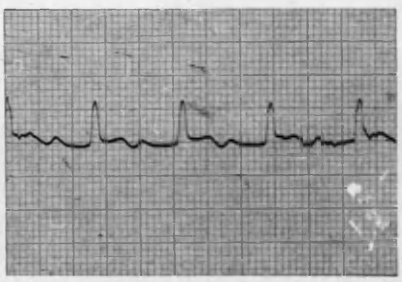
15 mins. after Hydrocortisone. Regular complexes but not sinus rhythm. Rate 120/min. (f)



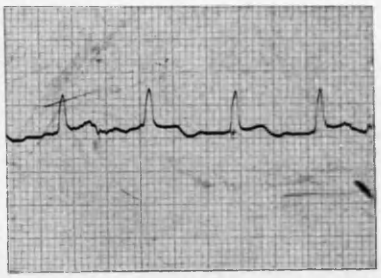
18 mins. after Hydrocortisone. P.R. now 0.26 sec. Rate 120/min. (g)



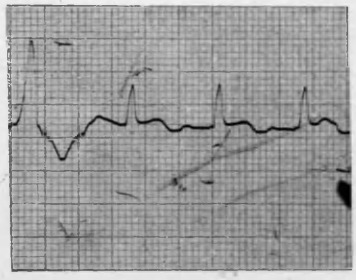
21 mins. after Hydrocortisone. P.R. now 0.24 sec. Rate 120/min. (h)



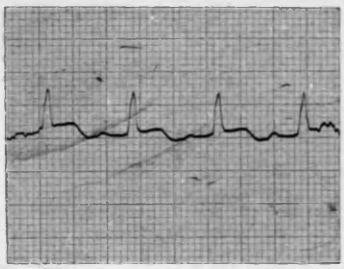
23 mins. after Hydrocortisone.
P.R. 0.22 sec.Rate 120/min. (i)



24 mins. after Hydrocortisone.
P.R. 0.20 sec. Rate 120/min. (j)



25 mins. after Hydrocortisone.
P.R. 0.16 sec. Rate 120/min. (k)



the hydrocortisone drip, there was a progressive decrease in the R.T. elevation until after twelve hours therapy the cardiogram would have passed for normal. Evidence of posterior ischaemia reappeared subsequently (Plate 7).

One of these cases occurred in special circumstances. This man (Case E.6) while being treated for pernicious anaemia in hospital collapsed in the ward, apparently dead. An immediate cardiogram showed the presence of ventricular fibrillation, and resuscitation was effected by external cardiac massage, thoracotomy, internal cardiac massage and electrical defibrillation. Following the shock, the cardiogram showed a posterior infarction with complete heart block (Plate 8). Hydrocortisone therapy was instituted and within forty minutes, sinus rhythm was restored. During the forty minutes, there was a progressive reduction in the degree of block similar to that noticed in the other heart block cases (Plate 8 a, b) and although a spontaneous recovery of this nature, following electrical defibrillation, cannot be excluded, an immediate return to the former rhythm is more usual (Semple & Dall, 1962) and for this reason, the effect is credited to the therapy given.

Of these nine cases, eight represent acute onset of heart block. In all of them, sinus rhythm was restored within 24 hours. One died (Case E.5) on the tenth day as a result of a mesenteric embolism, which occurred despite anticoagulant therapy. The mortality in this group wasreduced to 12.5%. There was no doubt that in this group the rate of return to sinus rhythm and the mortality rate were significantly different from the "untreated" cases, and the results indicated a direct relationship between the improved conduction and the administered hydrocortisone.

(D). Acute Heart Block - Untreated.

One case, observed before the steroid trial was started (Case G.2) illustrates the natural history of good prognosis with spontaneous, gradual recovery. 10 days after infarction, latent block replaced complete block, and on 16th day, sinus rhythm returned.

Case G.2 on the other hand was admitted as an acute myocardial infarction and treated as such; the fact that he had complete heart block was not noted until after his death on the second day.

Twenty five cases of heart block have been studied. Where the onset was acute, sinus rhythm has been restored by the use of steroid therapy, except in one case who died before the treatment could be effective. Where the block was of longstanding, the conduction could not be returned to normal, although two cases illustrated shortening of the P-R interval and increase in heart rate. Stokes-Adams attacks ceased after the start of steroid therapy.

2. Bundle-Branch Block.

This form of conduction defect was seen in 7 cases. 3 of these were in the acute heart block series (E.1; E.4; E.9); one was associated with a chronic heart block (F.6) and 3 occurred in the Trial cases, one control (B.13) and two of the steroid group (A.6 and A.8). In all three associated with complete block, the QRS pattern returned to normal during treatment of the heart block; the recovery taking up to 9 days. These consisted of one left bundle-branch block and two cases of right bundle-branch block.

The other 4 cases consisted of two who had previous records showing that the bundle-branch block pattern was not new; another in whom it was

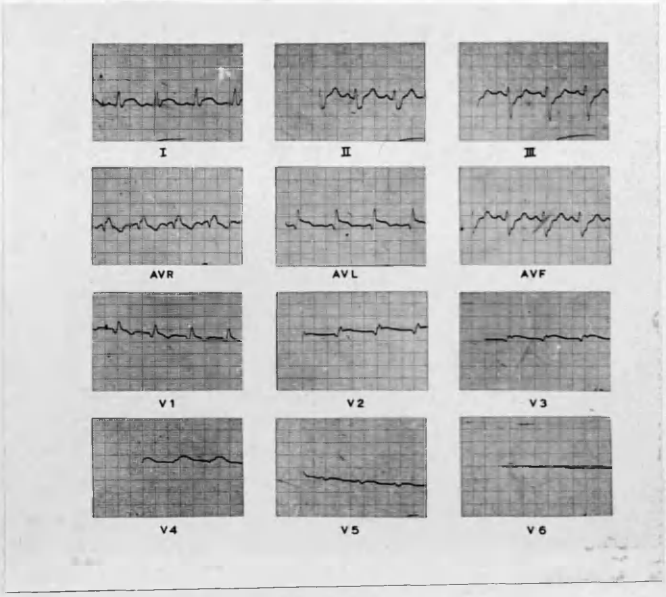
PLATE 9.

A.T.M.
(Case A5 and also E4)

(1) SHOWING INITIAL INFARCT PATTERN; (2) THE DEVELOPMENT OF COMPLETE HEART BLOCK WITH AURICULAR FIBRILLATION;

19.9.61

(1)



21.9.61

(3)

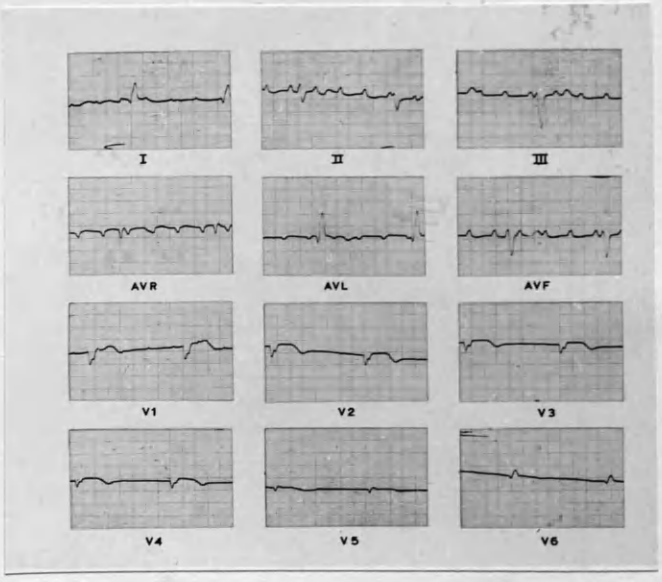


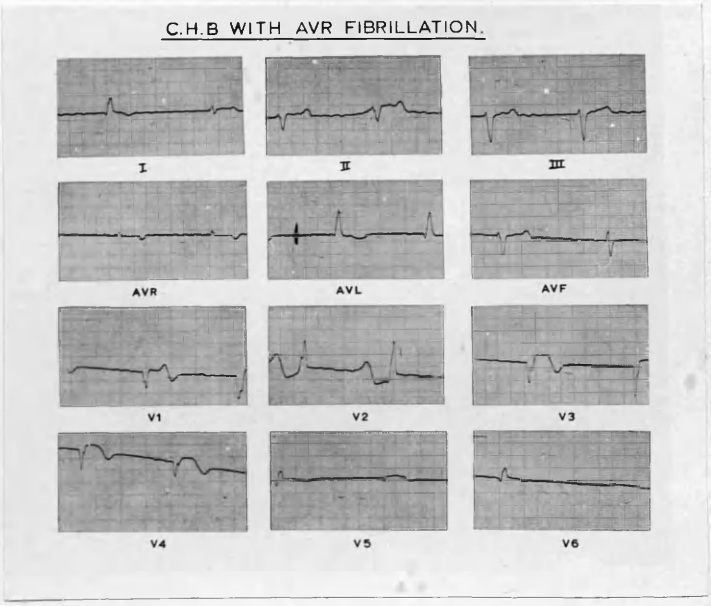
PLATE 9a.

A.T.M.
(Case A5 and also E4)

(3) THE REAPPEARANCE OF P WAVES, STILL WITH HEART BLOCK AFTER HYDROCORTISONE; AND (4) FINAL RESOLUTION TO SINUS RHYTHM.

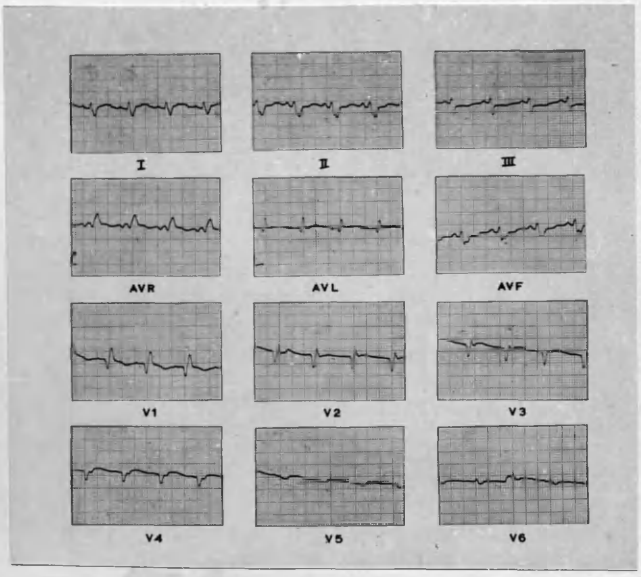
22.9.61. 2.15am.

(2)

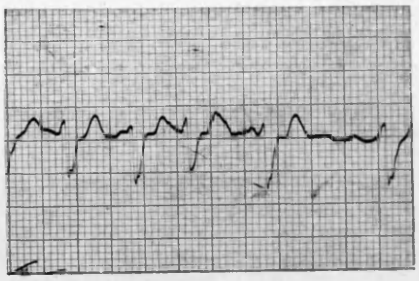


22.9.61.

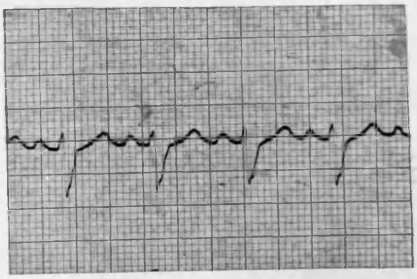
(4)



(a) After resusictation from an apparently dead state by external cardiac massage. Cardiogram shows auricular fibrillation 120/min. (Lead 2)



(b) 4 hours later after 100 mgms. hydrocortisone given intravenously. Sinus rhythm. (Lead 2).



associated with a longstanding heart block, and presumably old; and one (A.6) in whom the duration was not known. One of those with a previous record was a control case (B.13) in the Trial series, all the others had steroids, either for Trial, or for heart block. No change occurred in the pattern of these 4 cases, and bundle-branch block persisted.

3. Arrhythmia.

In the trial cases, auricular fibrillation appeared twice. Case A.5 (E.4) in which the fibrillation complicated complete heart block, and resolved quickly after the initial injection of hydrocortisone, before the heart block (Plate 9).

Case A.11, died on the twelfth day. On the tenth day he collapsed suddenly and had apparently died. External cardiac massage was carried out for ten minutes during which time respiration returned and the heart restarted. On recovery there was auricular fibrillation which had not been present previously. Following an injection of 100 mgms hydrocortisone intravenously, the rhythm returned to sinus complexes (Plate 10). Case F.6, with heart block and auricular fibrillation of longstanding showed an improved heart rate with steroids, but the arrhythmia was unaltered.

Auricular fibrillation of recent onset was abolished during steroid therapy, whereas chronic fibrillation was not influenced.

4. Trial Cases.

Twentyfive cases were treated with a hydrocortisone and prednisolone regime (Group A), and an equal number for a control series (Group B). Allocation to groups was by random numbers.

HYDROCORTISONE GROUP A.

Case	Age	Sex	QS	qR	Shock	Failure	Previous History.	Result
1. F.B.	53	M		+	+	-	Angina. Two years.	Home.
2. L.D.	66	M	+	-	-	+	Hypertension.	Died 14.
3. H.C.	71	F	+	-	+	+	Hypertension. 6 Years.	Died 3.
4. A.M.	65	F	+		-	-	-	Home
5. A.M.	46	M	+	-	+	-	-	Home
6. J.M.	65	F	+	-	+	+	Hypertension.	Died 6.
7. S.L.	60	F	+	-	+	+	Angina. 6 months.	Died 2
8. G.S.	74	M	+	-	+	+	Infarct. 5 Years.	Died 3.
9. H.S.	61	F	+	-	+	-	-	Home.
10. M.S.	50	F	+	-	+	+	Angina. 6 months.	Home.
11. J.G.	68	M	+	-	-	-	Angina. 3 months.	Died 12.
12. J.T.	58	M	+	-	+	+	Infarct 5 years.	Died 4.
13. R.M.	50	M	+	-	-	-	-	Home.
14. W.N.	52	M	+	-	-	-	Infarct 2 years.	Home.
15. H.S.	76	F	+	-	-	-	-	Home.

HYDROCORTISONE GROUP A.

Case	Age	Sex	QS	qR	Shock	Failure	Previous History.	Result
16. J.R.	58	M		+	-	-	Infarct. 3 months.	Died 5.
17. H.Y.	63	M	+	-	-	-	Angina. 2 years.	Home.
18. J.U.	41	M	+	-	+	-	-	Home.
19. F.H.	59	M		+		+	-	Home.
20. J.B.	56	M	+	-	-	-	-	Home.
21. P.C.	59	M	+	-	+	+	Angina. 1 year.	Home.
22. B.McK.	62	F	+	-	-	-	Hypertension.	Home.
23. J.S.	78	M	+	-	+	-	-	Home.
24. M.S.	67	F	+	-	-	+	Angina 2 years.	Home.
25. I.S.	58	F	+		+	+	-	Home.

CONTROLS. GROUP B.

Case	Age	Sex	Major	Minor	Shock	Failure	Previous History	Result.
1. A.G.	53	M	+		-	-	-	Home.
2. W.A.	51	M	+		-	-	-	Home.
3. M.W.	65	F		+	-	-	Angina. 3 years.	Home.
4. R.D.	44	M		+	-	-	-	Home.
5. D.F.	48	M	+		-	-	-	Home.
6. R.R.	51	M	+		+	+	M. Infarct. 3 years.	Died 2.
7. W.S.	68	M		+	-	-	M. Infarct. 8/52.	Home.
8. T.R.	71	M	+		-	-	Angina 2 years.	Home.
9. A.H.	58	M	+		-	-	-	Home.
10. J.B.	66	M	+		+	+	Angina 3/12.	Died 10.
11. J.W.	55	M	not	known	+	+	Prev. Infarct 10 years.	Died 1.
12. J.R.	58	M	-	+	-	-	Angina 6/12.	Home.
13. P.C.	64	M	-	+	+	-	Infarct 6/12.	Home.

CONTROLS. GROUP B.

Case	Age	Sex	Major	Minor	Shock	Failure	Previous History.	Result.
14. P.R.	65	M	-	+	-	-	-	Home.
15. J.F.	58	M	+		-	+	-	Home.
16. R.L.	51	M	-	+	-	-	M. Infarct. 5 years.	Home.
17. S.N.	65	M	-	+	-	-	M. infarct 8/12.	Home.
18. E.T.	44	M	-	+	-	-	C.A.D. Old Infarct.	Home.
19. M.B.	58	F	+		-	-	Angina 6/12.	Home.
20. A.S.	56	M	+		+	-	-	Died 3.
21. I.B.	40	M	+	-	-	-	Angina 1 year.	Home.
22. S.K.	41	F	-	+	+	-	Angina 1 year.	Died 1.
23. A.D.	56	M	+		+	+	Angina 1/12.	Died 11.
24. J.S.	57	M	+		+	+	Infarct 2 years.	Died 1.
25. S.B.	65	M	-	+	+	+	Infarct 1 year.	Home.

A further series of 100 comparable cases were studied to see whether the control group represented a fair sampling, and to ensure that the Trial regime had not caused an excess mortality among control cases (Group C.).

Sex Distribution.

In this Trial there were 13 female cases. There was a male/female ratio of $1\frac{1}{2}/1$ in Group A and 7/1 in Group B.

Age.

In Group A there was a mean age of 60.5 years; in males, 58.7 years (range 41 - 78) and in females 63.3 years (range 50 - 76).

In Group B, the mean age was 54.3 years; males 54.3 years (range 40 - 71) and females 54.6 years (range 41 - 65). The difference in age between the groups is almost entirely due to the larger number of females in Group A, as coronary artery disease tends to occur in females at a later age (Peel, 1955) (Table 10 A, B).

Clinical Features.

1. Shock.

In the treated group, 13 cases showed evidence of shock, including 5 of the 8 in this group who died, a mortality of 38.4%; in the control group, of 8 cases showing evidence of shock, 6 died, a mortality rate of 75%. In the absence of shock, a much lower death rate occurred, irrespective of other features. In Group A, three deaths occurred in twelve cases (25%) and in Group B one death in seventeen (6%) (Table 11A).

2. Failure.

In Group A, 11 cases showed some degree of failure and 6 died (55.5%); of the 14 other cases in this group only two deaths occurred (14.3%). In

TABLE 10. (A)

	GROUP A.			GROUP B.		
Sex	No.	Died	Mortality	No.	Died	Mortality
Male	15	5	33%	22	6	27.2%
Female	10	3	30%	3	1	33%
Totals	25	8	32%	25	7	28%

TABLE 10. (B)

	GROUP A.	GROUP B.
Male	58.7% (41-78) years	54.3% (40-71) years
Female	63.3% (50-76) years	54.6% (41-65) years
Average (all)	60.5 years	54.3 years

TABLE 11 (A).

EFFECT OF SHOCK ON SURVIVAL.

GROUP A.				GROUP B.			
Shock		Died	Mortality	Shock		Died	Mortality
Present	13	5	38.4%	Present	8	6	75%
Absent	12	3	25%	Absent	17	1	6%

TABLE 11 (B).

EFFECT OF FAILURE ON SURVIVAL.

GROUP A.				GROUP B.			
Failure		Died	Mortality	Failure		Died	Mortality
Present	11	6	55.5%	Present	7	5	71.4%
Absent	14	2	14.3%	Absent	18	2	11%

TABLE 12.

EFFECT OF PREVIOUS HISTORY ON SURVIVAL.

	GROUP A.			GROUP B.		
	No.	Died	Mortality	No.	Died	Mortality
Present	15	8	53.3%	17	6	35.2%
Absent	10	0	0.0%	8	1	12.5%

TABLE 12 (A).

EFFECT OF PREVIOUS HISTORY (TYPE).

	GROUP A.			GROUP B.		
Group	No.	Died	Mortality	No.	Died	Mortality
Prev. History.						
C.A.D.	11	5	45.4%	17	6	36%
Others.	4	3	75%	0	0	0.0%
All	15	8	53%	17	6	36%

TABLE 13.

EFFECT OF TYPE OF INFARCT ON SURVIVAL.

	GROUP A.			GROUP B.		
Major	22	7	31.8%	13	5	38.4%
Minor	3	1	33%	11	1	9%

2. Failure.

In Group A, 11 cases showed some degree of failure and 6 died (55.5%); of the 14 other cases in this group only 2 deaths occurred (14.3%). In the Control Group, of 7 cases with failure, 5 died (71.4%); of those with no failure (18) only 2 died (11%). (Table 11 B.).

3. Previous History.

15 Cases in Group A had a previous history of cardio-vascular disease, and all 8 deaths occurred in this Group (53.3%).

In the Control Group 17 cases had a previous history and of these 6 died (36%) leaving 1 death in 8 cases with no previous history (12.5%). (Table 12, 12A).

4. Type of Infarct.

22 cases in Group A had a major infarct 88%, and among these there were 7 deaths, a mortality of 31.8%. In the Control Group there were 13 major infarcts (52%) of whom 5 died (38.4%).

In a group of 3 with minor infarcts, 1 death occurred in the Treated Group (33%) and there was 1 death in 11 minor infarcts in the Control Group (9%). (Table 13).

Severity and Distribution of Cases.

Although cases of minor infarct occurred with shock, failure and a previous history of cardio-vascular disease separately, it was unusual for a combination of two or more features to occur unless there was a major infarct. The higher incidence of major infarcts in Group A has resulted in a higher proportion of severe cases in this group, despite the random selection techniques. This is seen in Table 14 where 10 cases (40%) occur

TABLE 14.

SEVERITY AND MORTALITY ACCORDING TO CLINICAL FEATURES.

DISTRIBUTION ACCORDING TO SEVERITY.

	GROUP A.				GROUP B.			
Score	4	3	2	1	4	3	2	1
No.	7	3	9	6	4	3	7	11
Died	5	1	1	1	4	1	1	1
Mortality	71%	33%	11%	16%	100%	33%	14%	9%
Distri-:bution.	10	9	6		7	7	11	
	40%	36%	24%		28%	28%	44%	

TABLE 15.

RELATION OF TYPE OF INFARCT AND PAST HISTORY.

	GROUP A.			GROUP B.		
	No.	Died	Mortality	No.	Died	Mortality
Major	13	7	53.8%	8	4	50%
Minor	2	1	50%	9	1	11%

in the severe grades 3 and 4 in Group A and 7 (28%) in Group B.

The overall distribution of cases in the Control Group is very similar to that of the cases in Group C, showing that according to the distribution in Group A, this group contains an excess of severe cases, in which a higher mortality rate is expected (Table 14). If an expected mortality is calculated for groups A and B from the mortality rates of Group C, according to the distribution of severe cases, then 10.1 deaths should have occurred in Group A where there were 8, and 7.69 deaths in Group B where there were in fact 7 deaths. So that although there is an impression that the treated cases had some benefit among the severe cases, the overall death rate is almost identical in the trial groups. In analysis of each of the clinical features separately, the same impression of slight benefit is gained in the treated groups although statistical tests show no significant difference between the results. Only in respect of past history did the Control Group have a lower mortality, and this is entirely due to the distribution of minor infarcts associated with this feature (Table 15).

CHAPTER 9.

EFFECT OF THERAPY ON RATE OF EVOLUTION OF INFARCT.

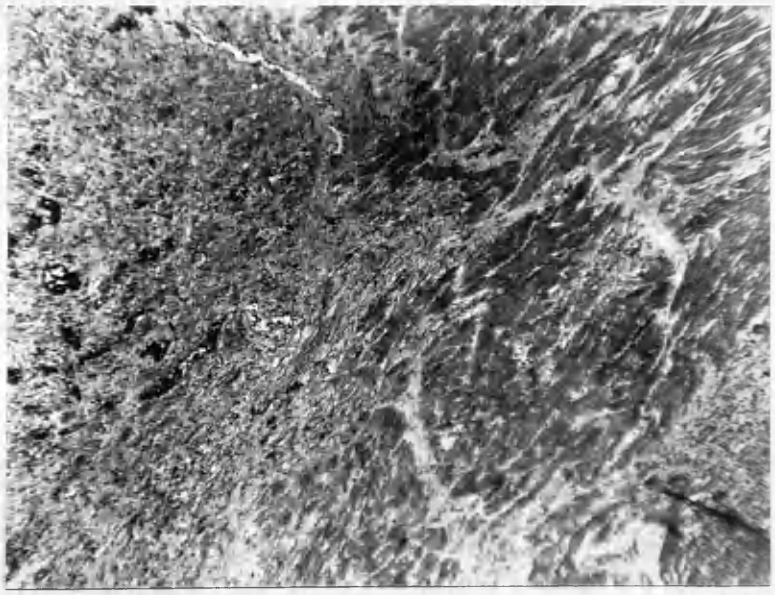
Action on myocardium.

Interpreted effect on cardiogram.

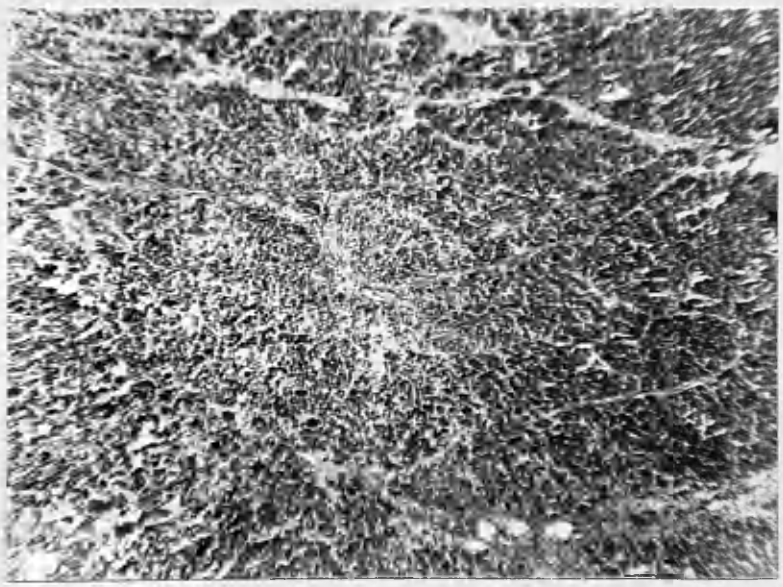
CHAPTER 9.

Effect on the Rate of Evolution of the Infarct.

The evolution and healing of myocardial infarcts in relation to the time after the acute injury has been recorded in detail (Cook, 1942; Mallory et al, 1939). The effect of steroid on the rate of repair has been variously reported. Chapman et al, 1952, noted"no deleterious effect upon the degree of fibrosis at the site of the infarct". Hepper et al, 1955 in confirming that there was no appreciable delay in healing, noted also that there was narrowing of the inflammatory reaction band round the infarct and some delay of phagocytosis of the necrotic muscle. Johnson et al, 1953 observed a marked decrease in the local fibroblastic prolification in the first fourteen days, with a sharply demarcated edge between infarcted area and adjacent muscle. At thirty days the differences were no longer apparent. These workers reported considerable reduction in the infarct size as a result of treatment. Post-mortem material has allowed an assessment of rate of healing during steroid therapy as compared with a normal response to infarct. Case C60 and Case E5, represent a pair. Both died on tenth day after infarct and both had a major infarct. The former occurred in the survey cases, the latter in the group of heart blocks, and therefore treated with a high dosage steroid regime. Histologically the difference between the two is striking, and is in keeping with the work of Johnson et al in that in the treated case there is a sharp line of demarcation with necrotic muscle and healthy muscle in apposition. The capillaries are thin walled and large without the surrounding cuff of cells seen in the "normal". The untreated case illustrates the more usual findings with a broad band



(a) Treated case (E5). Sharp line of demarcation between necrotic and healthy muscle. Minimal infiltrate. Large thin walled capillaries.



(b) Control case (C60). Broad band of interstitial oedema and cellular infiltrate between infarct and healthy muscle. Capillaries surrounded by a cellular cuff.

PLATE 12

Myocardial response to coronary artery occlusion.
(after Plotz)

N= Normal muscle. Isch.= Ischaemic zone

Inj.= Zone of Injury.

TABLE 16.

RATE OF EVOLUTION OF CARDIOGRAM IN DAYS.

GROUP A.			GROUP B.		
No. of Patients	Mean Values (days)	Standard deviation	No. of Patients	Mean Values (days)	Standard deviation
Major 16	14.50	± 7.05	Major 7	17.86	± 7.22
Minor 2	5.0	± 1.41	Minor 9	14.33	± 7.97

t = 1.85. Not significant.

of polymorphonuclear infiltrate lying between the necrotic muscle bundles and extending into the surrounding normal muscle (Plate 11). Of the cases in whom post-mortem was obtained, only one of the steroid group showed much evidence of polymorph infiltration and this was in the case of block which persisted. He died after only 12 hours therapy (300 mgm. hydrocortisone). The histology showed an infiltrate which could not have been differentiated from normal.

In further cases in whom large doses of steroids were employed, not included in the present work, autopsy has consistently shown a sharp demarcation between infarct and normal muscle (Plate 13).

In view of these features, it was considered that some acceleration in the evolution of the cardiogram might be apparent. This was strengthened by the return of the cardiogram to a normal pattern in one of the treated cases (E.2) during hydrocortisone drip therapy. It must be assumed that on the periphery of the infarct, there is a band of ischaemic tissue (Plate 12 after Plotz) and that this area is responsible for part of the cardiographic pattern. Any reduction in the size of the ischaemic zone might be reflected in a more rapid disappearance of the injury pattern and an overall reduction in the size of the infarct. The serial cardiograms of the trial cases were traced backwards from the final record to find the earliest point at which changes ceased to occur. In Group A, seventeen cases survived; one of the deaths was due to ventricular fibrillation in a case in whom the appearances of stable evolution presented on the tenth day. This has been taken as an evolved cardiogram with a second coronary incident causing the fatal arrhythmia two days later. In arriving at an average rate

of evolution, eighteen series of records have been examined for this group. In the Control Group B, one case had no cardiogram. In one with a minor infarct on top of previous episodes, determination of evolution was not possible with any certainty, and this case has been excluded from the calculation. Sixteen series of records have been examined in detail.

In Group A there were 16 major infarcts considered, with a mean rate of evolution for major attacks of 14.5 ($\pm$ 7.05) days. In Group B, 7 major infarcts and had a mean rate of 17.86 ($\pm$ 7.2) days. In Group A, 2 minor infarcts had a mean value of 5 ($\pm$ 1.41) days and in Group B, 14.33 ($\pm$ 7.97) days. (Table 16).

The difference between the groups is not statistically significant and lends no support to the suggestion of accelerated evolution of the cardiogram; on the other hand, neither does it signify any delay in evolution, a negative point, but one of some importance, since delay in phagocytosis of necrotic muscle has been suggested.

CHAPTER 10.

EFFECT OF THERAPY ON CONDUCTION.

P-R Interval.

Lown's Theory.

Effect on Transmission of Impulse.

As there were serial records, it was possible to observe throughout the trial the effect on the atrio-ventricular conduction time of steroid therapy.

The cases with initial heart block are not used in this survey as the first P-R interval obtained in these is under the influence of steroids, but in the trial series, it was possible to obtain an initial record prior to starting treatment.

The cardiogram has been examined initially, at the end of one week of steroid regime, and also the last record taken before discharge. This should give a pre-steroid reading, a reading from the mid-point of steroid therapy while on moderate doses, and a reading two to three weeks after stopping treatment.

The P-R interval was measured from the point at which the tracing departed from the isoelectric line at the start of the "P" wave, to the first deflection of the QRS complex. All measurements were made with dividers to allow maximum accuracy in assessing the second decimal figure.

Lown et al (1955) reported a shortening of the P-R interval, in the pathological state of steroid excess, Cushing's syndrome. Caramelli and Tellini (1961) graphed the duration of the P-R interval in a smaller number of cases during their observations, on cases of varying degrees of heart block. In this study, the observations are based on patients with normal conduction at the onset. The effect on latent heart block of long duration will be discussed later.

TABLE 17.

P-R INTERVAL GROUP A.

	Mean Values ± Standard deviation	No. of Patients.
Initial	0.1595± 0.02139	20
One week.	0.1485± 0.02231	20
Final.	0.1582± 0.01630	17

APPENDIX 17A.

	Mean Differences ± Standard error.	No. of Patients	Remarks
Initial - one week.	+ 0.011 ± 0.0044	20	Significant differ-:ence P<0.05.
Initial - Final.	0.000 ± 0.0038	17	No significant difference.
One week - Final.	- 0.013 ± 0.0048	17	Significant differ-:ence P<0.05

TABLE 18.

CONTROLS.

P-R INTERVAL. GROUP B.

	Mean Values ± Standard deviation	No. of patients.
Initial.	0.1586 ± 0.01864	21
One week.	0.1595 ± 0.02479	21
Final.	0.1544 ± 0.02202	18

APPENDIX 18 (a).

	Mean Differences ± standard error.	No. of Patients.	Remarks.
Initial - one week.	- 0.00095 ± 0.00437	21	Not significant.
Initial - Final.	+ 0.00389 ± 0.00545	18	Not significant.
One week - Final.	+ 0.00056 ± 0.00575	18	Not significant.

Once again the control series have provided a comparative series, so that the observation taken at one week can be compared with the initial and final records, and these in turn related to the control group. In all the records of 35 cases have been reviewed, 17 of these being treated cases (Table 17).

The control group showed a mean value of 0.158 secs. (range 0.12 - 0.18 sec.) on admission; the treated cases, a mean of 0.159 sec. (range 0.12 - 0.20 sec.) at the same period. On the 7th (or 8th) day record, the controls had a mean value of 0.159 sec. (range 0.12 - 0.20 sec.) and the treated, 0.148 sec. (range 0.12 - 0.16 sec.). The final value was 0.154 sec. (range 0.12 - 0.20 sec.) for controls, and 0.158 sec. (range 0.13 - 0.18 sec.) for the treated cases. (Tables 17, 18).

The constancy of the control mean value, and the mean value for the treated group initially, and finally, giving 5 out of 6 mean values at identical rate; the same mean rate as recorded by Lown et al, (1955) in 539 control subjects; throws into relief the shortening of P-R interval in the steroid treated cases, during treatment.

The figures show a statistically significant difference between the P-R interval at one week in the steroid treated cases compared with other readings indicating that there is acceleration of conduction in the A-V conducting tissue when on steroid therapy (Table 17 A, B; 18 A, B). The relationship of this to the mode of action of steroids in heart block will be discussed later.

CHAPTER 11.

COMPARISON OF EFFECT OF HIGH AND LOW DOSAGE REGIMES.

(a) Animal work.

(b) Present work - Heart Block Cases.

- Trial Cases.

Comparison of Dosage Regimes.

In preparing the regimes for this trial of therapy, the chief consideration was that no harm should result from the treatment. The dosage of hydrocortisone was based on the assumption that it might have to be given to patients in acute pulmonary oedema; although doses of up to 700 mgms in 24 hours had been used successfully in cases of heart block, even when badly shocked, it was decided to err if necessary on the side of underdosage. Accordingly, a scheme of hydrocortisone dosage was prepared to give 200 mgms in the first 24 hours after admission to hospital. This would yield a body weight dose of 3 mgm/Kgm (approximately) for a patient weighing 65-70 Kgm. In the cases of heart block treated, the dose of hydrocortisone used was determined by the clinical response, and in all cases considerably higher levels were reached than in the Trial series. A range from 400 - 700 mgms of hydrocortisone was used in the first 24 hours and this gives a body weight dosage scale ranging from 6 - 10 mgm/Kgm. Although not planned as such, these two groups of steroid treated cases represent a low dosage and a high dosage regime respectively and a comparison of the effects of the treatment on specific features yields information on the adequacy of the low dosage regime.

In the experimental work on animals, both high and low dosage regimes have been examined (Chapman et al, 1952; Opdyke et al, 1953; Hepper et al, 1955). Chapman et al (1952) used depression of the eosinophil count as a measure of the adequacy of cortisone dose. Initially they used 3 mgm/Kgm cortisone, but found 7 mgm/Kgm a more satisfactory level in later experiments.

Opdyke et al (1953) studied two groups of animals, treated with 10 mgm/Kgm cortisone by injection. Hepper et al (1955) compared the effect on infarct healing on dogs given 2.5 mgm/Kilo and 10 mgm/Kilo cortisone by injection, against control animals.

Johnson et al, did not use body weight dosage but gave a fixed amount of cortisone, either 12.5 mgms b.d. (low dosage) or 20 mgms b.d. (high dosage). Based on the average animal weight in each group treated, this represents a dosage scale of 0.75 mgms cortisone/Kgm (low and 1.1 mgm/Kgm. (high) which is well below the levels used by the other workers.

It will be observed that the doses used in the present work are not dissimilar to the standards of high and low dosage scales used by authors other than Johnson et al. Although the "weaning" course of steroid is identical in the two groups of steroid cases, they have been classed as high dosage where the first day of therapy included doses of 400 - 700 mgms hydrocortisone, and low dosage when on 200 mgms on that day. While differences in the myocardium between treated animal and control animals have been reported up to the 14th day, it was felt that, as if conduction could be restored in a case of heart block in less than 24 hours then the principle anti-inflammatory action may be established in the same time, and the differing doses employed during this critical phase determined the case as a high or low dose example.

In the group of cases treated because of heart block, the most striking feature is the rapid return of normal conduction once therapy is instituted. Heart block, bundle-branch block and auricular fibrillation all disappared when of recent onset. This contrasts with the trial group (GroupA) in which two cases developed heart block while on the prednisolone "weaning" course

(A.2; A.4). One of these returned to sinus rhythm without alteration of therapy; the other was given hydrocortisone as for heart block regime and returned to sinus rhythm. Thereafter the prednisolone was continued. Apart from two cases of bundle-branch block already described and one episode of auricular fibrillation (A.8) the only other abnormality of rhythm in this group was paroxysmal tachycardia, an episode of which occurred four days after stopping steroids (Case A.4).

It may seem contradictory that while steroids are being used to treat heart block on one hand, two cases of "block" appear in the group treated with steroid. A reason for this may be offered in a closer study of these cases.

Case A.2. was admitted to hospital after 36 hours of intermitting and incapacitating angina. He had a severe precordial pain radiating to the medial aspect of his left arm which lasted one hour. The clinical examination showed moderate hypertension, no shock, but crepitations at both lung bases. The initial E.C.G. was not diagnostic. He was regarded clinically as a "mild" infarct and included in the hydrocortisone group of the trial. After 48 hours, results of serum transaminase activity were reported in keeping with acute infarction. A second cardiogram on day 2 showed T inversion in posterior leads without abnormal Q waves and suggested posterior ischaemia without frank infarct changes. On the third day, the classical pattern of acute posterior infarct appeared, with latent heart block. Although the latent block resolved without altering the level of steroid dosage, the posterior infarct remained. Death occurred suddenly on the 14th day when the E.C.G. pattern was not changing, the blood pressure restored to 155/90 mm.Hg. and apparently good progress being

made. The autopsy showed a long thin antemortem thrombus completely occluding the right coronary artery. The vessel was itself extremely atheromatous and narrowed. In retrospect, the evidence suggests an initial thrombosis without infarct, followed by retrograde spread of thrombus almost to the mouth of the vessel, causing a gradually increasing area of damage, which would include the septal vessel from the right coronary artery to the conducting tissue. In this case, thrombus formation occurred despite adequate anticoagulant therapy, and was largely related to the atheromatous state of the vessel wall. An infarct was virtually unavoidable whatever therapy was employed, and the latent heart block was a part of the infarct picture because of the site of thrombus.

(Case A5/E4). This man was admitted with a story of precordial pain and shock. The initial cardiogram gave evidence of a subendocardial infarction in the anterior wall. After the routine therapy for this group of the trial, he was improving, when a sudden collapse with severe shock heralded another episode. The cardiogram showed complete heart block with auricular fibrillation. A further course of hydrocortisone (600 mgms in 24 hours) resulted in return of auricular complexes and disappearance of block and the E.C.G. now revealed a transmural anterior infarct with right bundle-branch block which subsequently cleared to leave the infarct pattern alone (Plate 9). It is suggested here that as the posterior leads were normal throughout, this patient is one of the 5% in whom the blood supply to the conducting tissue arises from the left coronary artery (Ball, 1933) and thus the block is associated with an anterior infarct which developed slowly over the first three days of observation.

It appears therefore that these two cases are those in whom the site of infarct imperilled the blood supply to the conducting tissue. In both, the infarct picture was slow to develop in the cardiogram. The low dosage steroid therapy did not prevent the infarct from occurring, or the resultant arrhythmia becoming established; but in the second case the adoption of high doses of steroid therapy abolished the block.

CHAPTER 12.

DISCUSSION.

Discussion.

The principle objectives of this study have been:

1) to report the use of steroid therapy in cases of heart block associated with myocardial infarction;

2) To see whether there might be a place for steroid therapy in the management of acute infarction;

3) To assess where circumstances allowed, the effect on the healing of an infarct;

4) To evaluate the theories of the mode of action of steroids, with particular reference to heart block.

1. Heart Block.

The incidence of heart block is variously quoted, depending on whether all degrees of block are included. Latent heart block is not infrequently seen after acute infarction, sometimes as a transient state in the first week, sometimes developing during the healing phase (up to third week). In this latter circumstance it is apt to be persistent, more so than the higher grades of block. Unlike the higher grades of block, latent block is not usually associated with any particular area of injury in the septum (Plotz). Partial and complete heart block are usually, though not exclusively, observed with posterior infarction resulting from an occlusion of the right coronary artery, from which the branch to the conducting tissue arises (Ball, 1933; Schwartz, 1936; Gilchrist, 1958). An incidence of 1.5% for complete heart block has been reported from collected series of acute infarcts (Kerr, 1937; Master, 1938). Condry and Thomson, 1957 reported an incidence of 3.3% which is in agreement with the

findings of Vialard (1950) who collected the finding from 2,583 cases of infarct in the literature. In a similar review of literature referring particularly to heart block, 42 cases were described from 2,132 patients with acute infarct, an incidence of 2% (Dall & Buchanan, 1962). Since Rosenbaum and Levine (1941) reported an incidence of 2.4%, it is obvious that the incidence has remained fairly constant for 25 years despite improving technique of diagnosis, and more frequent detection of milder grades of infarction. It is curious that while the comparatively minor upset of latent block is often permanent, the natural history of complete heart block is a tendency to return to the original rhythm, and usually within six to fourteen days of the infarct (Gilchrist, 1958).Penton et al (1956) have stated that if a patient is in sinus rhythm prior to the onset of complete heart block as a result of infarct, return to the former rhythm should be expected, and persistence of the block is unusual. Most authorities are of the same mind (Rosenbaum & Levine, 1941; Rowe and White, 1958; Bell & Pardee, 1930; Gilchrist, 1958). Many case reports describe the gradual evolution from complete heart block to normal conduction by stages (complete - partial - latent - sinus rhythm) in periods ranging from a few days (Gilchrist, 1958; Ball, 1933) to a month (Rowe and White, 1958) or even eight weeks (Bell and Pardee, 1930) after the acute infarction. In the face of this evidence of natural recovery, the need for therapeutic measures with potent steroids is not obvious, especially as it has been observed earlier that in one group treated orally (Group D), the rate of recovery from block did not appear to differ greatly from the expected rate. However, despite the general opinion that the prognosis is good for those surviving the acute phase, there is a considerable mortality to be faced in the early days following

the precipitating infarction. Penton et al (1956) in reporting 49 cases, showed that 23 regained their former rhythm with the normal convalescent period, but 21 died in the early days. Similarly Condry (1957) records eight deaths in fourteen cases in the first three days after infarct; Gilchrist (1958) eleven deaths in twentyfive patients; Master et al (1938), five deaths in six cases. These reports indicate the need for some therapy in the early stages to reduce the mortality. From 165 cases reported in the literature, we find an overall mortality rate of 45%. In his collected series (1950) Vialard reports 58% mortality for complete heart block, and it is agreed by others that the immediate prognosis for complete heart block is not good (Plotz, Master, 1938; Mintz & Katz, 1942; Applebaum & Nicolson, 1933).

In the group of cases with heart block reported, all these features are demonstrated. Case G1, illustrates a spontaneous recovery from complete heart block after infarction, in the space of 16 days, having passed through 2/1 block (5th day) and latent block (10th day) during recovery. Case G1 on the other hand represents the poor prognosis, with death occurring within 36 hours of infarction, complete block being persistent throughout.

In Group D, on oral steroid therapy, a mortality of 42.5% remains, although, only two of the three deaths were of cardiac origin. Nonetheless, one of the deaths, only twelve hours after starting treatment illustrated the need for measures more rapidly effective. This has taken the form of intravenous hydrocortisone administration, and in Group E, in nine cases treated, the therapeutic effect of restoring normal conduction was achieved in a few hours. The only failure was shown subsequently to have had a

previous infarction involving the septum, so that in this case the block was not of acute onset, and therefore from our experience not likely to respond. Although the group is small, of the remaining eight cases, only one died; this death ten days after the infarction was due to a massive mesenteric embolism, and was not the result of a further cardiac upset. It would appear that intravenous steroid therapy restores normal conduction, and does so rapidly at a time when considerable urgency exists, as the mortality is high only while the block is present, and the prognosis improves with the conduction.

Before any therapeutic regime can be taken as useful and acceptable, it must be sufficiently simple and practicable to permit its use in the circumstances in which the condition to be treated commonly arises. Further, there should be no harmful effect from the therapy. In this trial, four cases were returned to sinus rhythm after the initial hydrocortisone injection, and before the intravenous infusion was started. While this form of regime has been used for convenience, and continued for the sake of uniformity, we do not feel, now, that the infusion is necessary, if hydrocortisone can be given at frequent intervals. Faced with infarction and complete heart block in domiciliary practice, therapy can be initiated at once and continued in hospital, or could, if necessary, be carried out entirely in the bedroom, the only apparatus required being a syringe, needle and hydrocortisone. While electrocardiography is helpful in estimating progress, and indeed for diagnosis in some cases, almost all, even those with pulse rates of 50 - 60 per minute when in block show a definite upward step in the pulse rate when the conduction becomes normal; this can be appreciated without a cardiogram.

The technique then, is reasonably simple and requires the minimum of equipment.

The side effects which may be produced, particularly as very large doses of steroid may be used are not without potential danger, but in this study, no serious complication arose to cause interruption of therapy. The risk of provoking seizures in epileptics can be overcome by a temporary increase in the suppressive therapy. The increased risk of thrombo-embolic complications (Crossgriff) is based on scant evidence, and in this context is covered by anticoagulant therapy. Perforation did not occur, but one man with no history of peptic ulcer or liver disease died of a severe gastro-intestinal haemorrhage (D.7) which could be attributed to steroids or anticoagulant therapy, or a combination of both. Fluid retention was not troublesome throughout the trial except where renal function was impaired.

Following occlusion of a coronary artery, the degree of myocardial recovery depends on the balance between the extent of arterial narrowing and the rate and extent of the development of vascular anastomosis (Smith & Papp, 1957). In many instances, there is from the onset an area of complete infarction, with muscle fibres which will undergo necrosis. Surrounding this, is an area of injury in which the balance between blood supply and requirement is finely adjusted, and the survival or necrosis undecided. More distant from the centre of the infarct, on the periphery of the whole area of injury is a zone of inflammatory reaction and tissue oedema which shades off from the area of injury into healthy myocardium. In this zone are the capillaries which must form the anastomoses necessary to increase the blood supply to the area to assist recovery. The experimental work of Johnson et al (1953) showed that pretreatment with steroids not only

reduced the size of an induced infarction, but also, increased the inter-coronary capillary anastomoses. While animal experiments in healthy dogs, cannot be directly interpreted as applicable to middle-aged human subjects with atheroma and degenerative coronary artery disease, interest in this work was aroused by the fact that in the cases of heart block treated, and in those reported in the literature (Table 3.) the likelihood of restoring conduction to normal appeared to rest on the presence of an acute injury. Since interarterial anastomosis on the septum is known to exist in 80% of hearts (Blumgart et al, 1950) and persists in the presence of coronary artery disease in more than 50% (Blumgart et al, 1950) the bundle tissue is favourably placed for recovery. It is assumed that in some cases at least, the ischaemia of the septum which results in heart block, is contributed to by the hypotension associated with the acute myocardial injury, (Plotz, M., 1957); and without any alteration in the actual vascular state, the correction of hypotension may result in improved conduction. Apart from this, block will arise when the conducting tissue is embraced by:

1) The area of necrotic tissue,

2) The area of ischaemia,

3) Or the zone of inflammatory reaction.

Since those who do not die in the acute stages of heart block tend to recover normal conduction it is probable that the existing vascular cover of the conducting tissue is sufficient to prevent complete infarction, although in one report, of 28 survivors, 5 had persisting heart block (Penton et al, 1956). In the natural process of recovery, the congestion and interstitial oedema is gradually reduced over the first 7-10 days, and capillary proliferation into the area begins toward the end of the first

week (Cook, 1942; Mallory et al, 1939; Lodge-Patch, 1951). It is about this time interval that spontaneous improvement in cases of heart block is noted (Gilchrist, 1958). It seems probable that these facts are related and that the speed of recovery is governed by the degree of infiltration and oedema, and by their prejudicial effect on the blood supply to the injured area. If the anti-inflammatory effect of cortico-steroids can accelerate dispersal of the infiltration and oedema, this will improve the blood supply through existing capillaries, and allow earlier proliferation of new vessels, thereby improving the prospects of recovery in tissue which is injured, perhaps ischaemic, but not as yet necrotic. It is our experience that under the influence of steroids, the recovery of normal conduction from complete heart block, can be accelerated to hours, instead of days if the drug is given intravenously or intramuscularly (Prinzmetal,(1954); Friedberg et al (1960)). When therapy is given orally, there is still a shortening of the waiting period before recovery, but this is less obvious (Caramelli & Tellini, 1961; Dall & Buchanan, 1962). The discrepancy between oral and intravenous regimes rather points to a critical level of steroid before the effect is seen. In this reasoning, heart-block is used as a convenient example, since the onset is detectable and its disappearance is recognisable so that rate of recovery can be seen easily. In eight cases of acute infarct with heart block, the injury, or ischaemia of the conducting tissue causing the block was relieved in a matter of hours and in one case, all trace of a posterior myocardial infarction was eliminated from the cardiogram during the intravenous hydrocortisone therapy, only to return later when steroids were being withdrawn. On the other hand, in six cases

of chronic coronary artery disease with heart block, normal conduction could not be restored, emphasising the fact that only at the site of a recent block, where there is inflammatory reaction can this effect be expected.

Trial Cases.

If the same reasoning could be applied to myocardium other than the conducting tissue, there should be reduction of the band of inflammatory oedema round the infarct, and improved blood flow to the area, within twentyfour hours, instead of seven days, a fact which should enhance the prospects of recovery in areas where the blood supply is critical after the acute injury. Plate 11A shows a section of the myocardium from one of the hydrocortisone cases who died (Case E.5) compared with control case of equivalent duration (Plate 11B). The former shows necrotic tissue, the infarct, in close opposition to normal healthy myocardium, with a sharp line of demarcation. The other shows an area of infarct, an area of healthy muscle and between these a broad band of muscle densely infiltrated with polymorphonuclear leucocytes, an area where survival is still in doubt. It is in this area, that the therapy would have an opportunity of salvaging tissue which might otherwise become part of the infarct, or at least develop ischaemic fibrosis and become a source of frequent incapacitating angina.

To test this theory, a controlled trial has been undertaken to see whether hydrocortisone treatment would:

1) improve survival rates after acute infarction,

2) lead to a more rapid evolution of the cardiogram, and perhaps some reduction in the area of infarction.

Random selection did not provide a comparable distribution of cases between the groups, and a further study was carried out to obtain information

on the expected mortality, and the features which are primarily concerned with mortality. By means of this it was possible to show that the distribution of severe, average and mild infarcts into the control group was not significantly different from that anticipated, but there was a significant imbalance between the percentage of severe and mild cases, with an undue proportion of severe cases in the hydrocortisone group (Table 14, 15A). Despite this excess, the overall mortality rates for groups A, B, and C are almost identical, and although no difference can be shown statistically, the clinical impression is that a greater number of deaths were expected in Group A than did occur, and that the hydrocortisone regime was of most value in the very severe case with shock and failure.

The first of the two criteria of the test has not been satisfied in that no significant improvement on the survival rate has been shown. This indicates either:

(a) that hydrocortisone has no effect, or

(b) that the dosage used was insufficient (compared with the higher doses used in heart block), or

(c) that what effect has been achieved is due to a different mode of action such for example as a non-specific supportive effect in cases with shock.

Certainly this last explanation could explain the slight, but not significant differences in survival of the very severe infarcts in the hydrocortisone group. In the heart block series, shock and hypotension did present, but not in all cases, and in some cases (E1, E2 and E6) the rhythm was normal before the last traces of shock were gone; indeed it appeared that the recovery of sinus rhythm banished the shock, rather than the reverse. It

seems likely that while hydrocortisone does have sustaining properties of value in the treatment of shock, this is a secondary action, and the discrepancy between the successful therapy in the heart block cases, and the lack of effect in the trial series is related to the differing doses used in the two groups.

The evolution of the cardiogram has proved to be an extremely difficult point to evaluate, since a surprising variation can be observed if cardiograms are taken at sufficiently frequent intervals. No significant difference could be shown in the rate of evolution of the cardiogram in Group A as opposed to Group B.

The second aspect of this trial of therapy has shown no statistically significant difference in the rate of evolution in the cardiogram between the two groups studied.

The third aspect explored was the correlation between experimental work, and the effect in man as observed in post-mortem material; to see whether infarcts pursued the normal evolutionary changes; and to see whether any delay in healing of the infarct area occurred. The standard changes and rates of change in the myocardium after infarction have been well established (Cook, 1942; Mallory et al, 1939; Lodge-Patch, 1951) and attention has been concentrated on the steroid treated cases. The autopsy report of one "untreated" case from the survey (Case C.60) is paired with one of the heart block series (Case E.5) for age, sex and duration of infarct and the histology compared (Plate 10). Experimental work has suggested that during steroid therapy the inflammatory reaction after infarct is greatly reduced, and what does exist is rapidly dispersed. A delay in phagocytosis of the dead muscle at fourteen days (Hepper et al; 1955; Johnson et al, 1953),

with healing indistinguishable from controls at thirty days (Chapman et al, 1952; Johnson et al, 1953) has been reported. Considerable reduction of polymorphonuclear leucocytic infiltration was observed, with a sharp edge of demarcation between the infarct and healthy muscle, and some reduction of local fibrous tissue production at fourteen days (Johnson et al), Sound healing at 30 days was the experience of all, and no case of cardiac rupture has been reported. Baker and Whitaker (1950) showed that locally applied steroid therapy impeded healing, but with systemically administered steroids in a dose of 1 mgm/Kgm. Ragan (1949) observed no lack of healing.

In the post-mortem material available information can be derived about the first fourteen days from the cases which comprise this trial, but another case, not in the trial, who died following a second infarction after having continuous steroid therapy for ten weeks following his initial attack, gives evidence of the adequacy of healing while on steroid therapy (Plate 13). These specimens show marked reduction in the expected inflammatory reaction and polymorphonuclear infiltrate. This is well illustrated by direct comparison of the "paired" cases. The treated case (E.5) shows an area of necrosis with negligible infiltration, and a sharp line of demarcation from the normal muscle. The amount of fibroblast activity is probably rather less than would be expected ten days after infarction. The capillaries are wide and have no surrounding cellular "cuff". The pair (C.60) section shows the customary pattern of a broad band of leucocytic infiltration between the area of necrosis and the area of healthy muscle, the dividing band shading off gradually into each, and no line of demarcation. There is active proliferation of fibroblasts and phagocytosis of the necrotic muscle. It will be noted how closely these features resemble the reported histology

PLATE 13

(a) Showing occluded coronary artery; dense fibrosis at site of old infarct(top left); healthy area below artery.

(b) Showing fresh haemorrhagic infarct(left) in apposition to former infarct scar.

from the experimental work. Delay in phagocytosis of the infarct and depression of fibroblast proliferation could lead to thin walled scar tissue, and ventricular aneurysm could well result. Follow up of these cases, up to fifteen months has shown no change in heart size or shape, even where large doses of steroids were used.

Plate (13 .) was taken from the left ventricle of a man who had ten weeks continuous hydrocortisone therapy after an extensive anterior infarct, and an episode of ventricular fibrillation from which he was resuscitated. Despite continuous steroids, the healing of the former infarction has taken place, and sound scar tissue occupies almost the full thickness of the ventricular wall. The area shown illustrates a coronary vessel almost totally occluded, the area of former infarction well healed, with adequate fibrous scarring, and a small area of normal myocardium.

Adequate healing can take place even with continuous steroid therapy throughout the healing phase.

No information has been derived about the size or extent of the infarcts, but all the other features detailed in the animal work have been observed, and indicate an anti-inflammatory action at the site of injury.

Mode of Action in Heart Block.

Three theories exist in this context, and the circumstances governing the theories has been the different type of case treated and the varying results achieved.

When Prinzmetal's original case was reported, the experimental work in dogs (Chapman et al 1952 ; Johnson et al 1953) was just published, and the anti-inflammatory theory agreed well with the similar effect in cases of rheumatic fever who developed conduction disturbances.

The impressive collection of cases published (Lown et al, 1955) established the second theory - the "facilitation" of conduction in the bundle tissue. Since this work did not concern cases of myocardial damage, or indeed cases of heart block of any degree, any interpretation of this in the cases of infarct, with heart block must be guarded. In Lown's cases there was either excess adrenal steroid (Cushing's) or deficiency (Addison's) and the common yardstick was the rate of atrio-ventricular conduction along an intact bundle of His. In the cases of coronary artery disease with block there is abnormal transmission of activity through the injured or ischaemic bundle tissue (latent block or partial block) or no direct transmission at all (complete block). In the latter circumstances, "facilitation" will be of little value if there is no longer an intact system through which electrical activity can be "facilitated". For this reason, I feel this theory can have little bearing on the action in complete heart block. In latent or in partial heart block, however, there is either a delay in transmission of the atrio-ventricular impulse, or an inability of the bundle to accept all the atrial stimuli. That steroids have the ability to shorten the P-R interval in circumstances where neither endocrine upset nor conduction defect complicate the issue, has been shown in this work, and in a case of long-standing block, the P-R interval was shortened from 0.28 sec. to 0.24 sec. Since this was a long-standing latent heart block, the likelihood of an anti-inflammatory effect is remote. On the other hand, all the cases of block, during the phase of recovery, illustrated a pattern of decreasing degree of block - complete to partial, partial through serial changes 5 to 1, 4 to 1, etc., to latent block, and

then to normal (Case E.1) which could be interpreted as evidence of an increasing degree of "facilitation", but the behaviour does not bear this out. In the case of latent heart block, and in the trial cases, when the steroid was withdrawn, the P-R interval increased to the starting level; in the cases of block treated, the result obtained persisted without maintenance therapy. A return to normal by removal of the abnormal feature, in this case tissue ischaemia, rather than any acceleration of conduction dependent on the therapy.

The same reasoning can be used when considering Friedberg's theory of "arousal" of the ventricular pacemaker. In his cases, the most striking therapeutic effect was the abolition of Stokes Adams attacks and increase in the pulse rate after starting steroids. In a series of six cases, this occurred in all, whereas of four cases who returned to normal rhythm, three lapsed into block when treatment was stopped, and sinus rhythm could not again be restored. It is not surprising that he took as the primary effect, the inhibition of Stokes-Adams attacks by an improved auricular ventricular ratio and an increase in the pulse rate. One case in Group F (6) illustrates this type of reaction; he was admitted to hospital with auricular fibrillation and Stokes-Adams attacks. Stokes-Adams attacks ceased after 48 hours therapy, and the cardiogram showed a ventricular rate increasing progressively for 40 to 100 per minute. During reduction of prednisolone therapy the pulse rate has fallen steadily in parallel and at a maintenance level of 10 mgm. daily, the apical rate is 56 per minute with auricular fibrillation. No further Stokes-Adams attacks have occurred.

In this case the effect has been ventricular acceleration, without any change in rhythm. The apical rate is closely tied to the dose of steroid employed, and Friedberg's ventricular arousal theory may be fairly quoted as a mode of action since the duration is of long-standing, and there is unlikely to be much inflammatory tissue to be dispersed. Lown's theory is not applicable in that there is no measurable P-R interval.

The work reported here shows that complete heart block is rapidly and readily relieved by intravenous steroids and, that histologically, there is rapid diminution in the inflammatory reaction round the infarct during steroid therapy. The resolution of complete heart block associated with acute myocardial infarct has been shown to take place by an orderly and progressive reduction in the degree of block similar to but faster than the steps observed in spontaneous recovery; the only difference is in the rate at which resolution of the block occurs. In this circumstance the restoration of sinus rhythm is not regarded primarily as a direct effect of steroids on the conducting tissue but the rapid return of normal function to this tissue is attributed to the accelerated dispersal of the inflammatory oedema and infiltration which accompanies infarction.

It has been shown, also, that steroids increased the rate of conduction in the bundle of His as suggested by Lown et al, and Caramelli and Tellini. This does not appear to be a theory in contradiction of the anti-inflammatory mode of action, but rather a complimentary effect which, taken with Friedberg's "arousal" theory, probably indicates a generally increased sensitivity of the conducting mechanism. In chronic block, where little anti-inflammatory action can be expected, this secondary effect will increase the rate of

conduction and increase the ventricular rate, but not as a rule achieve normal conduction. This effect alone appears to be sufficient to stop Stokes-Adams attacks.

CONCLUSION:

The use of intravenous hydrocortisone and oral prednisolone in cases of myocardial infarction has shown an alteration in the histological appearances which is due to the anti-inflammatory action of the hormones. This effect has been utilised in cases where heart block results from an acute infarction, and it has been possible to restore normal conduction in a matter of hours using the intravenous therapy and thus reduce the mortality rate.

In a controlled trial of therapy in acute infarction without heart block a lower initial dosage was employed. This trial has shown no significant difference in the rate of evolution of the cardiogram, or in the survival rate, but significant acceleration of P-R interval is present when on steroid therapy.

SUMMARY.

1. The effect of steroid hormones on conduction defects following myocardial infarction, has been studied.

Seven cases were treated with oral therapy and nine with intravenous therapy. Normal conduction was restored in all but two.

Six cases of heart block, not of recent onset, have been studied and the differing effect of steroid hormones in these circumstances observed.

The natural history of "acute" heart block has been illustrated by the "untreated" cases.

The theories of the mode of action have been examined, and evaluated in the light of the findings.

2. A controlled trial of steroid therapy in acute myocardial infarction is reported. This gives an impression that the therapy improves the prognosis in the severe case, but the results are not statistically significant.

3. Observations from post-mortem material are similar to the reports of work in experimental animals.

4. The effect of steroid on the P-R interval of the cardiogram has been evaluated on patients without conduction defects or endocrine upset, and confirms the existing literature.

APPENDIX I.

SUMMARIES OF CASE REPORTS.

TREATED GROUP OF TRIAL.

GROUP A.

F.B. (M. 53 years). (Casesheet 162176).

Admitted 18.7.61. Discharged 17.8.61.

On admission complained of severe retro-sternal pain lasting two hours associated with sweating and breathlessness. Had experienced anginal symptoms for about two years.

On admission moderately shocked but not dyspnoeic. The skin was cold and clammy but there was no cyanosis or jugular venous congestion.
B.P. 120/90 mm.Hg. Pulse 92 per minute and regular.
The heart sounds appeared normal. There was no adventitia at the lung bases.

Serum Transaminase:

	Day 1	Day 3	Day 6
S.G.O.T.	10	15	52
S.G.P.T.	18	18	18

E.C.G. showed a minimal posterior infarct with RT elevation in leads 2, 3 and aVF.

Progress - Evolution progressed rapidly and the cardiogram was evolved on the 2nd day.
Discharged well to continue anticoagulant therapy.

L.D. (M. 66 years). Casesheet 167031).

Admitted 12.9.61. Discharged 25.9.61.

Admitted with frequent angina of 48 hours duration culminating in a severe attack of chest pain lasting two hours. No previous history of angina but has been under treatment by his own doctor for mild hypertension for one year.

On admission he was in severe pain, but was not shocked. B.P. 170/115 mm.Hg. Pulse rate was 88 per minute and regular. The heart sounds were pure, but soft and heard with difficulty. There were crepitations heard at both bases but no other evidence of cardiac embarrassment. Other systems were normal.

E.C.G. - On admission showed T wave change in the posterior leads only.

Serum Transaminase:

	Day 1	Day 3
S.G.O.T.	18	90
S.G.P.T.	17	31

Progress - On clinical evidence included in the trial series. On the third day after a further mild attack of pain the cardiogram showed an acute injury pattern in the posterior leads with the presence of Grade I heart block, the P-R interval being 0.36 secs. The prednisolone course was not altered

and the latent heart block resolved in 48 hours. He then appeared well and had no further complaints until he died suddenly on the 14th day.

Post-mortem examination showed complete obstruction of the right coronary artery by fresh thrombus with gross atheromatous change in the vessel.

H.C. (F. 71 years). (Casesheet 17454).

Admitted 12.12.61. Died 15.12.61.

Complained on admission of severe left sided chest pain radiating down the left arm of five hours duration with gradual deterioration.
Has been treated for high blood pressure for six years.

On admission pale and breathless with increased jugular venous pressure and cyanosis.
B.P. 160/90 mm.Hg. Pulse 80 per minute, regular and of fair volume.
Both heart sounds are heard but are distant.
Basal crepitations are present in both lungs.

Progress - Died on the third day although the signs of initial cardiac failure had by that time cleared.
Hydrocortizone regime with anticoagulant therapy.

Serum Transaminase:

	Day 1.
S.G.O.T.	22
S.G.P.T.	16

E.C.G. - Acute antero-septal infarction not evolved.

A.M. (F. 65 years). (Casesheet 154938).

Admitted 6.5.61. Discharged 19.6.61.

Admitted with severe pain in the chest and left shoulder radiating down the left arm of 6 hours duration.

No previous history of cardio-vascular disease.

On admission no evidence of shock or cardiac failure.

B.P. 130/90 mm.Hg. Pulse 90 per minute, regular, with occasional extrasystoles.

Lung bases clear and no abnormality in other systems.

Progress - Uneventful after admission.

On Hydrocortisone regime and Warfarin throughout.

Serum Transaminase:

	Day 3	Day 6
S.G.O.T.	19	34
S.G.P.T.	9	28

E.C.G. - Acute antero-septal infarct. Cardiogram evolved rapidly and appeared stable at third day. Subsequent changes occurred during the third week after withdrawal of steroid therapy.

A.M. (M. 46 years). (Casesheet 176560).

Admitted 19.9.61. Discharged 19.10.61.

Complained of continuous pain radiating between shoulder blades and into both arms. The pain came on while walking. There was no previous chest pain or cardio-vascular illness.

On admission was distressed and in severe pain with moderate shock and slight cyanosis.

B.P. 125/100 mm.Hg. Pulse 110 per minute.

Heart sounds scarcely audible. No pericardial friction.

No basal crepitations.

No abnormality in other systems.

Serum Transaminase:

	Day 1	Day 6
S.G.O.T.	73	40
S.G.P.T.	54	57

E.C.G. On admission showed a right bundle-branch block with antero-septal infarct.

Progress - Started on hydrocortisone regime. On third day collapsed and showed severe shock. Cardiogram showed complete heart block with auricular fibrillation. Intravenous hydrocortisone started and within an hour the fibrillation was gone, but the heart block picture remained. 600 mgms Hydrocortisone given throughout the next 12 hours. Sinus rhythm restored

within 12 hours but right bundle-branch block persists. Bundle-branch block gone eight days later during the prednisolone regime and did not recur.

Discharged well to continue anticoagulant therapy.

J.M. (F. 63 years). (Casesheet 173824).

Admitted 2.12.61. Died 8.12.61.

Admitted with severe chest pain of about 6 hours duration and gave a history of angina of effort of three years duration.

On admission she was moderately shocked with slight increase in venous filling in the neck and marked cyanosis.
B.P. 130/100 mm.Hg. Pulse 98 per minute and regular.
The heart sounds were inaudible. There were crepitations present at both bases. Other systems were normal.

E.C.G. showed an extensive anterior infarct with multiple extrasystoles. There was also a right bundle-branch block.

Progress - Death occurred as the result of a rather unexpected deterioration on the 6th day when to that point her progress had been satisfactory.

S.L. (F. 60 years). (Casesheet 174241).

Admitted 7.12.61. Died 8.12.61.

Admitted with severe retro-sternal pain of 24 hours duration.
Gave a history of angina of effort of six months and diabetes mellitus of 8 years.

On admission grey and shocked with cold, clammy skin amd moderate cyanosis.
B.P. 105/70 mm.Hg. Pulse 150 per minute and regular.
Heart sounds inaudible.
Crepitations heard at both bases.

E.C.G. showed an acute antero-septal infarct.

Progress - Treated with hydrocortisone regime. State of shock improved rapidly and she appeared to be making good progress. The following morning she had a further episode of collapse from which she could nct be resuscitated.

G.S. (M. 74 years). (Casesheet 168818).

Admitted 5.10.61. Died 7.10.61.

Admitted with severe breathlessness on exertion and arrhythmia. There was a previous history of myocardial infarction five years ago but no conclusive history of pain related to the immediate admission.

On admission he was dyspnoeic and distressed with marked jugular venous congestion and cyanosis. There was no oedema.
B.P. 120/90 mm.Hg. Pulse 98 per minute and regular.
The heart is enlarged to the left the apex being in the sixth interspace, $5\frac{1}{2}$" from the mid line. There was triple cardiac rhythm but no murmurs and no pericardial friction. Bilateral basal crepitations were present and hepatomegaly two finger breadths.

Serum Transaminase:

	Day 2
S.G.O.T.	210
S.G.P.T.	240

E.C.G. showed right bundle-branch block which had existed in the records taken five years before. There was in addition an acute antero-lateral infarction.

Progress - He remained in left failure despite diuretic and Hydrocortisone therapy and died on the third day.

H.S. (F. 61 years).

History of epilepsy (petit-mal) - taking Phenobarbitone, gr. 1 b.d. No prior history of chest pain until infarct.

On admission complained of severe chest pain over precordium. Not radiating to arms. Severely shocked and dyspnoeic on admission but no objective evidence of failure present.

C.V.S. - B.P. 100/85 mm.Hg. Pulse barely perceptible, 80 per minute, regular, low tension, poor volume. Heart sounds distant but seemed pure.

Other systems - Reflexes brisk. Some weakness right arm and right leg with dysphasia.

E.C.G. - Evolved 19 days.

Progress - Recurrence of epileptic fits on 9th day. Up to 6th fits daily. Dose of anticonvulsant increased daily to Phenobarbitone gr. 1, t.i.d. and Mysoline 1 cap. b.d. Fits controlled on this therapy - transferred to convalescent ward after five weeks treatment. Died suddenly after further chest pain 10 days later.

Hydrocortisone regime for 16 days. Anticoagulant therapy throughout.

M.S. (F. 50 years). (Casesheet 166940).

Admitted 12.9.61. Discharged 15.10.61.

Complained of severe retro-sternal pain which came on during exertion on the morning of admission and which lasted 6 hours.
Has been treated for hypertension and has had angina of effort for at least six months.

On admission pale, shocked looking, with cold, clammy extremities although B.P. 140/100 mm.Hg., and Pulse 48 per minute and regular (no heart block).
Heart sounds inaudible.
Fine crepitations throughout both lung bases.
Other systems normal.

Progress - Had two further episodes of severe pain after admission without alteration in the cardiogram.
Otherwise progress uneventful on Hydrocortisone regime and Warfarin therapy.

Serum Transaminase:

	Day 1	Day 3
S.G.O.T.	58	18
S.G.P.T.	18	25

E.C.G.: Acute posterior infarct. Evolved 6th day with subsequent change during third week after withdrawal of Hydrocortisone.

J.G. (M. 68 years). (Casesheet 168531).

Admitted 1.10.61. Died 12.10.61

On admission had precordial pain on effort of three months duration with severe precordial pain at rest during the past 17 hours.

On admission he was pale but not obviously shocked. There was no cyanosis, and no jugular venous congestion.
B.P. 135/90 mm.Hg. Pulse 70 per minute and regular. The heart sounds are pure with no clinical cardiac enlargement.
There were no adventitia at the lung bases.

E.C.G. - antero-septal infarct.

Progress - Without incident until tenth day when he collapsed suddenly and apparently died. He was resuscitated with external cardiac massage and was found to have auricular fibrillation when the cardiogram was next taken. Following an injection of Hydrocortisone sinus rhythm was resumed within 4 hours. A further episode of cardiac arrest occurred 48 hours later from which he could not be resuscitated.

J.T. (M. 58 years). (Casesheet 160162).

Admitted 24.6.61. Died 27.6.61.

Admitted with severe chest pain of four hours duration.

Previous history of myocardial infarction five years ago.

On admission pale, ill-looking man with a thready pulse and cold, moist extremities. Jugular venous pressure raised.

B.P. 105/80 mm.Hg. Pulse 88 per minute and regular.

Heart sounds of poor quality and heard with difficulty. Widespread crepitations throughout the lung fields and particularly at the bases.

Other systems normal.

Progress - Resuscitated after admission and appeared to be improving, but died suddenly on the fourth day.

Serum Transaminase:

	Day 1.
S.G.O.T.	35
S.G.P.T.	20

E.C.G. - Old antero-septal infarct with fresh lateral infarct.

Not evolved.

R.M. (M. 50 years). (Casesheet 159986).

Admitted 23.6.61. Discharged 26.7.61.

Complained or recurring severe pain in the lower chest and upper abdomen of four hours duration.

No previous history of any cardio-vascular disease.

On admission he looks well. There is no evidence of shock or cardiac failure.

B.P. 130/80 mm.Hg. Pulse 64 per minute and regular.

Heart sounds of good quality. No crepitations are heard at the lung bases.

There is no abnormality in the other systems.

Progress - Uneventful on Hydrocortisone and Warfarin.

Serum Transaminase:

	Day 1.
S.G.O.T.	53
S.G.P.T.	32

E.C.G. - Developed appearances of antero-septal infarction slowly.

Cardiogram evolved at 11 days.

W.N. (M. 52 years). (Casesheet 167396).

Admitted 17.9.61. Discharged 20.10.61.

Admitted with a story of severe retro-sternal pain on the previous day and also on two occasions each of several hours duration on the day of admission. Previous myocardial infarction two years.

On admission is not shocked and shows no evidence of cardiac failure. Occasional crepitations are heard in the left lung but are related to cough and probably not failure.

Progress - Was troubled by dyspepsia and had buffered Prednisolone for the latter part of regime. Warfarin given throughout.

Serum Transaminase:

	Day 2	Day 6
S.G.O.T.	110	10
S.G.P.T.	45	17

E.C.G. - Acute antero-septal infarct. Evolved 22 days.

H. S. (F. 76 years). (Casesheet 168588).

Admitted 3.10.61. Discharged 13.11.61.

Complained on admission of severe retro-sternal pain which wakened her from sleep and lasted several hours.

Had been previously well.

On admission anxious and restless but not shocked and showing no evidence of cardiac failure.

B.P. 125/80 mm.Hg. Pulse 80 per minute and regular.

Heart sounds faint with a "tic-tac" quality. No basal crepitations audible.

Other systems normal.

Progress - Uneventful on Hydrocortisone regime and Warfarin.

E.C.G. - Acute antero-septal infarction. Evolved in 24 days.

J.R. (M. 58 years). (Case sheet 158560).

Continuing angina since infarct four months previously.
Severe chest pain persisting at rest, with only partial relief from Trinitrin or Morphine injection 36 hours prior to admission.

On admission not shocked. No jugular venous congestion, cyanosis or oedema.
B.P. 96/65 mm.Hg. Pulse 98 per minute, regular, poor volume, low tension. Heart not enlarged. Sounds pure but first sound almost inaudible at mitral area. No friction; no triple rhythm. Lung bases clear.
Other systems normal.

E.C.G. - Old posterior infarct with recent lateral extension. Not evolved.

Serum Transaminase:

	Day 3	Day 5
S.G.O.T.	78	74
S.G.P.T.	31	45

Progress - Acute left ventricular failure on third day with fall in blood pressure to 85/60 mm.Hg. and pulse 120 per minute. Dyspnoea persisting despite therapy. Urinary output poor - 18 oz. in 24 hours.
X-ray (day 4) - Acute pulmonary oedema.

H.Y. (M. 63 years). (Casesheet 159917).

History of mild angina of effort for two years. On day of admission had severe pain in back between shoulder blades and radiating round the rib cage to lower sternum and upper abdomen. No dyspnoea, nausea or vomiting. No sweating.

On admission he was in considerable pain but not shocked and not dyspnoeic. No jugular venous congestion. No oedema.

C.V.S. - No cardiac enlargement. Sounds of good quality and pure; no murmurs or friction audible.

B.P. 130/60 mm.Hg. Pulse 80 per minute, regular, good volume.

Other systems normal.

E.C.G. - Evolved 12 days.

Serum Transaminase:

	22/6	26/6
S.G.O.T.	16	66
S.G.P.T.	18	41

Progress - Continued to have episodes of pain in back and left chest for eight days. Thereafter progress was uneventful.

Hydrocortisone regime for 16 days. Anticoagulants given and continued after discharge.

J.U. (168477). M. 41 years.

Well until day of admission. Sudden onset of severe retrosternal pain after playing a game of table tennis.

On admission - Pale, cold, clammy and sweating with rapid shallow respiration. No jugular venous congestion or hepatomegaly. No oedema.

C.V.S. - Heart sounds distant and scarcely audible. No friction. B.P. 100/75 mm.Hg. Pulse 98 per minute and regular, poor volume and low tension.

Progress - Recovered from shocked state after 100 mgm. Hydrocortisone. Developed small pulmonary infarct at left base on 5th day. Signs cleared gradually over the following two weeks. Otherwise uneventful.

Hydrocortisone regime for 16 days. Anticoagulant therapy continued after discharge.

Transaminase -	30/9	2/10
S.G.O.T.	149	136
S.G.P.T.	96	22

E.C.G. - Evolution 20 days.

F.H. (M. 59 years). (Casesheet 160159).

Well until wakened from sleep at 4 a.m. by severe retrosternal pain and dyspnoea. Vomited soon after waking. No previous angina or exertional dyspnoea.

On admission not shocked or cyanosed by moderately dyspneeic with bilateral basal crepitations. Jugular venous congestion present. No oedema or hepatomegaly.

C.V.S. - No cardiac enlargement. Distant heart sounds, with coarse pericardial friction rub over lower half of precordium.

B.P. 120/60 mm. Hg. Pulse 96 per minute and regular; good volume.

E.C.G. - Evolved four days.

Progress - Pericardial friction gone on third day. Basal crepitations no longer present after one week. No pyrexia.

Hydrocortisone regime for 16 days. Anticoagulants continued after discharge.

J.B. (M. 56 years). (Case sheet 172760).

Well in every respect until stricken by severe, gripping retrosternal pain, not affected by position or breathing. Tingling sensation in both arms. No shock or collapse. Pain lasted 2 hours.

On admission comfortable. No cyanosis or evidence of cardiac embarrassment.

C.V.S. - Heart sounds of good quality and pure, but first sound is of less intensity than second.

B.P. 120/80 mm.Hg. Pulse 72 per minute and regular, good volume.

Other systems normal.

E.C.G. - Evolved 12 days.

Progress - Uneventful. Hydrocortisone regime for 16 days. Anticoagulant therapy continued after discharge home.

Serum Transaminase:

	19.11	21.11	23.11
S.G.O.T.	160	156	72
S.G.P.T.	35	96	80

P.C. (M.59 years). (Casesheet 159445).

Anginal symptoms for one year prior to admission.

Admitted with very severe pain of $2\frac{1}{2}$ hours duration across chest and into both arms.

He was cold, clammy and extremely dyspnoeic. Slight jugular venous congestion present; no oedema.

C.V.S. - No cardiac enlargement.

B.P. 120/80 mm. Hg. Heart sounds virtually inaudible; pulse 120 per minute and regular, small low tension pulse. Bilateral basal crepitations present. Liver two finger breadths below costal margin a distinct edge is felt.

E.C.G. - Evolved 5 days.

Serum Transaminase:

S.G.O.T.	123
S.G.P.T.	37

Progress - When pulse slowed a gallop pr triple rhythm was present. Diuretic therapy with Saluric was achieved satisfactorily and failure did not progress. Uneventful convalescence; up and home. Well after five weeks. Hydrocortisone regime for 16 days. Anticoagulants continued after discharge.

B.McK (F. 62 years). (Casesheet 171509).

Admitted 4.11.61. Discharged 8.12.61.

On admission had severe chest pain of 5 hours duration. Gave a history of hypertension treated by her own doctor for many years and increasing breathlessness on exertion in the past 12 months.

On admission her colour was good and although in severe pain there was no evidence of shock or cardiac failure present.
B.P. 220/135 mm.Hg. Pulse 80 per minute and regular. Triple rhythm present at the apex of the heart. Otherwise the sounds were normal. No basal crepitations were heard. Other systems normal.

E.C.G. showed a transmural antero-septal infarct.

Progress - Blood pressure fell to 140/90 mm.Hg. but her condition remained satisfactory apart from the transient appearance of crepitations at the right base on the third day. This cleared without the addition of diuretic therapy.
Anticoagulant therapy was given throughout and a course of hydrocortisone was given over the first 16 days.

J.S. (M. 78 years). (Casesheet 173818).

Well until four years ago. Increasing dyspnoea on exertion since. No previous chest pain or anginal symptoms. No dyspeptic symptoms. Sudden onset of severe upper abdominal pain radiating into lower chest; vomited once - food material only.

On admission he was in great pain, cyanosed and moderately shocked. There was cyanosis of lips, ears and finger nails. No clubbing of fingers. C.V.S. - No jugular venous congestion. No oedema. No cardiac enlargement. B.P. 150/100 mm.Hg. Heart sounds normal but muffled. Pulse 94 per minute with frequent extrasystoles, moderate volume and low tension; vessel wall is palpable but not rigid. Other systems normal.

E.C.G. - Evolution; 15th day.

Serum Transaminase:

	2.12	5.12.	6.12	
S.G.O.T.	22	31	30	Not diagnostic.
S.G.P.T.	5	10	15	

Progress - Uneventful stay in hospital for $7\frac{1}{2}$ weeks. Given anticoagulant therapy for the duration of his stay in hospital then this therapy was discontinued gradually.

Hydrocortisone regime as described used in first 16 days.

M.S. (F. 67 years). (Casesheet 175479).

Admitted after 24 hours of severe chest pain with ache in left arm. Angina for two years - increasing frequency for one month.

On admission B.P. 180/100 mm.Hg. Pulse 98 per minute and regular. Heart sounds inaudible. Jugular venous congestion +. Crepitations at both lung bases.

Progress - Had respiratory infection during third week, otherwise convalescence was uneventful.

Serum Transaminase:

	Day 2	Day 3	Day 16
S.G.O.T.	80	68	10
S.G.P.T.	31	49	30

E.C.G. - Evolved 28 days.

I.S. (F. 55 years). (Casesheet 176289).

Admitted 11.1.62. Discharged 17.2.62.

On admission complained of severe pain across the chest and between the scapulae of 18 hours duration. Apart from a premonitory discomfort two days prior to admission while climbing a hill there was no history of cardio-vascular disease.

On admission was mildly shocked. There was jugular venous congestion. B.P. 115/85 mm.Hg. Pulse 120 per minute and regular. Heart sounds were barely audible the first sound being slightly muffled.
The liver edge was palpable two finger breadths below the costal margin. There were crepitations audible at both bases.

E.C.G. - Evidence of an extensive transmural antero-septal infarct.

Progress - Cardiogram extended to embrace all anterior chest leads during evolution. Despite anticoagulant therapy there was an episode on the 12th day and again on the 33rd day when she appeared to have minor pulmonary infarctions on the left side.

APPENDIX II

SUMMARIES OF CASE REPORTS

CONTROL GROUP OF TRIAL.

GROUP B.

A.G. (M. 53 yrs) . (Casesheet 167634)

Admitted 20.9.61 Discharged 24.10.61.

Admitted with severe retro-sternal pain radiating down both arms and into the abdomen of 2 hours duration.

No previous history of chest pain or breathlessness on exertion.

No previous cardio-vascular disease.

On admission he is not shocked and there is no evidence of cardiac decompensation. His colour is good.

B.P. 130/70 mm.Hg. Pulse 80 per minute and regular and the heart sounds well heard and pure.

No basal crepitations on auscultation of the lung fields.

Other systems normal.

Progress: Uneventful. Convalescence over four weeks on anticoagulant therapy. Continued anticoagulant therapy after discharge.

Serum Transaminase:

	Day 1	Day 5
S.G.O.T.	20	25
S.G.P.T.	16	86

E.C.G. - Acute posterior infarct. Cardiogram evolved by sixteenth day.

W.A. (M. 51 years). (Casesheet 164219).

Admitted 12.8.61 Discharged 14.9.61.

Complained of severe pain in the sternal area of 7 hours duration on the day prior to admission. No previous history of breathlessness on exertion or chest pain.

No previous cardio-vascular disease.

On admission there is no evidence of shock. There is no cyanosis. There is no evidence of cardiac decompensation.

B.P. 130/70 mm.Hg. Pulse 72 per minute and regular, and of good volume. Both heart sounds are well heard and normal. No basal crepitations in the lung fields.

Other systems normal.

Progress: Mild recurrence of lower sternal discomfort for one hour three weeks after admission, banished by Trinitrin. Otherwise normal convalescence with anticoagulant therapy.

Serum Transaminase:

	Day 2.
S.G.O.T.	51
S.G.P.T.	49

E.C.G. - Acute antero-septal infarct. Cardiogram evolved on the fourteenth day.

M.W. (F. 65 years). (Casesheet 162349).

Admitted 20.7.61 Discharged 21.8.61.

Complained of severe retro-sternal pain of sudden onset while walking. Pain radiated up into the neck and left arm and was associated with sweating and breathlessness. Pain has persisted until admission.
She has had angina of effort for four years.
Known mild hypertensive for two years.

On admission slightly pale but not shocked in appearance and no dyspnoea.
No evidence of cardiac embarrassment.
B.P. 165/110 mm.Hg; Pulse 76 per minute and regular.
Both heart sounds well heard. No pericardial friction.
Good air entry at the lung bases with no abnormality.
Other systems normal to clinical examination.

Progress: One episode of positive occult blood was obtained during four weeks anticoagulant therapy which was subsequently discontinued. Otherwise convalescence uneventful.

Serum Transaminase:

	Day 1.
S.G.O.T.	20
S.G.P.T.	15

E.C.G. - Minor posterior infarct with QR change. Cardiogram evolved sixteenth day.

R.D. (M. 44 years). (Casesheet 165804).

Admitted 30.8.61. Discharged 4.10.61.

Complained on admission of intermitting chest pain of 48 hours duration with a severe attack of pain lasting 1½ hours on the day of admission. No history of previous cardio-vascular disease.

On admission no evidence of shock or cardiac failure.
B.P. 120/60 mm.Hg. Pulse 80 per minute and regular. Heart sounds well heard with no pericardial friction. Occasional rhonchi only on auscultation of the chest.
Other systems normal.

Progress: Uneventful with no further pain after admission.

Serum Transaminase:

	Day 1	Day 3
S.G.O.T.	9	18
S.G.P.T.	31	24

E.C.G. - Antero-septal minor infarction with RT and T wave changes. Cardiogram appeared to have evolved at 8 days but subsequently showed further evolutionary changes in the antero-septal leads.

D.F. (M. 48 years). (Casesheet 168732).

Admitted 3.10.61 Discharged 9.11.61.

While playing golf on the day of admission he developed severe chest pain of a constricting nature which forced him to stop. Any effort produced an exacerbation in his discomfort. He vomited shortly after the onset of the pain.

No previous history of angina of effort, breathlessness on exertion, or any cardio-vascular disease.

On admission flushed, apprehensive but not exhibiting shock.

No cyanosis and no evidence of cardiac decompensation.

B.P. 130/75 mm.Hg.; Pulse 90 per minute, regular and of good volume.

The first heart sound is distant but the sounds are pure. No adventitia at the lung bases.

Other systems normal.

Progress: Convalescence uneventful with anticoagulant therapy.

Serum Transaminase:

	Day 3.
S.G.O.T.	63
S.G.P.T.	40

E.C.G. - slowly developing antero-septal infarct. Cardiogram evolved in twentyeight days.

R.R. (M. 51 years). (Casesheet 166159).

Admitted 4.9.61 Died 5.9.61

Complained of intermittent crushing pain in the chest of 15 hours duration with two severe prolonged attacks. Pain did not radiate.

There is a previous history of coronary thrombosis three years ago.

On admission he is severely shocked, cyanosed, with moist, cold extremities and a thin, thready pulse.

B.P. 85/50 mm.Hg.; Pulse rate 124 per minute, regular.

Heart sounds almost inaudible. No friction or murmurs heard.

Crepitations present at both lung bases.

No abnormality in other systems.

Progress: Slight improvement with sedation but remained dyspnoeic and hypotensive until death.

Intravenous Aminophyllin and Chlorothiazide given with no response.

Serum Transaminase:

	Day 1.
S.G.O.T.	76
S.G.P.T.	57

E.C.G. - Acute anterior infarction. Cardiogram had not evolved.

W.S. (M. 68 years). (Case sheet 162720).

Admitted 26.7.61; Discharged 9.9.61.

Admitted with severe chest pain of increasing intensity over 36 hours. Myocardial infarction eight weeks previously.

On admission in moderately severe pain, but not shocked and no evidence of cardiac failure. There is no cyanosis.
B.P. 150/100 mm.Hg. Pulse 100 per minute, regular of good force and volume. Heart sounds are of poor quality and the first sound is scarcely audible. No pericardial friction. No crepitations are heard at the lung bases. Other systems normal.

Progress - Frequent and recurring attacks of anginal discomfort for three weeks. Thereafter gradual improvement and convalescence extended for two weeks beyond the normal span.

Serum transaminase:

	Day 2	Day 15	Day 19
S.G.O.T.	91	60	38
S.G.P.T.	80	56	76

Repeated because of further pain.

E.C.G. - Acute posterior infarction with QR change. Evolved on twentysixth day,

T.R. (M. 69 years). (Casesheet 116196).

Admitted 23.7.61. Discharged 11.9.61.

Complained of severe chest pain associated with tightness and pain in the left arm on the day before admission with recurrence on the day of admission.
Has had symptoms of angina of effort for two years.
No other cardio-vascular disease.

On admission he is slightly pale, but not shocked and not distressed.
There is no cyanosis or cardiac decompensation.
B.P. 110/70 mm.Hg.; Pulse 92 per minute, regular and of fair volume.
Heart sounds are normal and pure. Occasional rhonchus at both bases.
Otherwise lung fields clear.
Other systems normal.

Progress: Despite anticoagulant therapy had several further episodes of epigastric discomfort and lower chest pain.

Serum transaminase:

	Day 2.
S.G.O.T.	115
S.G.P.T.	49

E.C.G. - Acute posterior infarct. Cardiogram evolved on eighth day.

A.H. (M. 58 years). (Casesheet 162543.)

Admitted 23.7.61. Discharged 23.8.61.

Well until two days before admission when he developed transient episode of tightness across the chest. On the day of admission was wakened from sleep with severe precordial pain and tingling in the left arm which lasted for five hours.

No previous cardio-vascular disease.

On admission there is no evidence of shock, cyanosis or cardiac decompensation.

B.P. 120/70 mm.Hg. Pulse 68 per minute and regular. Heart sounds are normal and there is no cardiac enlargement. The lung bases are clear. Other systems normal.

Progress - Uneventful. Convalescence - on anticoagulant therapy.

Serum Transaminase:

	Day 1.
S.G.O.T.	134
S.G.P.T.	14

E.C.G. - Ischaemic change, initially, developing antero-septal infarct. Evolved twentysix days.

J.B. (M. 66 years). (Casesheet 165118).

Admitted 23.8.61. Died 2.9.61.

Complained of a constricting feeling around the chest radiating into the left arm, as a tingling sensation of 17 hours duration.
Has a previous history of intermittent claudication, hypertension and angina of three months duration.

On admission he was pale, distressed and cyanosed with cold, clammy skin and severe shock.
B.P. 130/80 mm.Hg. Pulse 130 per minute, regular, of low amplitude and tension. There is slight increase in the heart size to clinical examination. Presystolic triple rhythm is present at the cardiac apex. Shower of crepitations at both lung bases. Liver edge is palpable three finger breadths below costal margin and tender.

Progress - After initial improvement over the first five days, his blood pressure which had been improving fell again and sudden collapse occurred on the tenth day with ? ventricular fibrillation and death.

Serum Transaminase:

	Day 1.
S.G.O.T.	56
S.G.P.T.	21

E,C.G. - Acute posterior infarction. Had not evolved.

J.W. (M. 55 years). (Casesheet 160108).

Admitted 26.6.61. Died 26.6.61.

Complained of sudden severe chest pain two hours before admission and present on admission.

Previous myocardial infarction ten years ago.

On admission profusely shocked with cold, clammy extremities, profuse sweat, cyanosis and marked jugular venous congestion.

B.P. unrecordable. Pulse barely perceptible, 120 per minute and regular.

Heart sounds inaudible.

Crepitations present at both bases.

Other systems normal.

Died before cardiogram taken.

J.R. (M. 58 years). (Casesheet 158560).

Mild angina of effort for six months.

Very frequent chest pain for 48 hours prior to admission; during one of these he lost consciousness.

On admission pale, anxious, but not perspiring and not dyspnoeic.

No jugular venous congestion or oedema. No cyanosis.

B.P. 96/60 mm.Hg. Pulse 60 per minute, regular, low tension.

Sounds poorly heard. No murmurs audible. Lung bases clear.

Other systems normal.

Progress - Uneventful.

Serum Transaminase:

	Day 2
S.G.O.T.	80
S.G.P.T.	39

P.C. (M. 64 years). (Casesheet 154017).

Admitted 8.11.61. Discharged 9.12.61.

Complaint of central chest pain of increasing severity for 48 hours. Previous history of acute posterior infarct six months ago.

On admission pale and sweating with slight cyanosis. No cardiac decompensation.
B.P. 140/90 mm.Hg.; Pulse 80 per minute and regular. Heart sounds pure and no murmurs or friction audible. No adventitia at the lung bases. Other systems normal.

Progress - Exhibited multiple extrasystoles during the convalescence period which responded to Quinidine, grs. 3, four times daily. This was continued on discharge. Anticoagulant therapy given throughout.

Serum Transaminase:

	Day 1	Day 2.
S.G.O.T.	110	195
S.G.P.T.	25	70

E.C.G. - Posterior infarct and left bundle-branch block. ? acute antero-septal infarct. Cardiogram still showing alterations in the posterior leads at twentyeight days.

P.R. (M. 65 years). (Casesheet 163487).

Admitted 4.8.61. Discharged 7.9.61.

Complained of severe retro-sternal pain of almost 12 hours duration, partially relieved by an injection of Pethilorphan.
No previous history of angina of effort, breathlessness on exertion or any cardiac disease.
Mild hemiparesis one year ago.

On admission not shocked, no cyanosis and no evidence of cardiac decompensation. Mild finger clubbing present.
B.P. 105/70 mm.Hg. Pulse 92 per minute and regular.
Heart sounds normal. Occasional coarse crepitations heard at the right lung shifting on coughing. Liver two finger breadths enlarged; firm and not tender.

Progress - Uneventful from the cardiac point of view. X-ray of chest shows a bronchiectatic segment in the right lower lobe with a coin shaped lesion in the right axilla. E.S.R. 2 mm. in one hour (10.8.61); 2 mm. in one hour (18.8.61).

E.C.G. - Slowly developing subendocardial posterior infarct.
No change after 7 days.

J.F. (M. 58 years). (Casesheet 174859).

Admitted 16.12.61. Discharged 17.1.62.

Complaint of intermittent tightness in his chest for four days followed by the onset of severe chest pain on the morning of admission.
No history of cardio-vascular disease.

On admission looks ill, is cyanosed and has marked jugular venous congestion but there is no shock.
B.P. 120/75 mm.Hg. Pulse 96 per minute, regular and of good volume.
Heart is not enlarged to clinical examination. The heart sounds are of poor quality and there is marked pericardial friction best heard at the fourth left interspace. Persistent crepitations are heard at the left base.
Other systems normal.

Progress - After initial improvement had a sudden recurrence of congestive cardiac failure on the eighth day after which signs of a pulmonary infarction became apparent; this despite anticoagulant therapy. After this there was steady improvement until the time of discharge.

Serum Transaminase:

	Day 1	Day 2	Day 3
S.G.O.T.	224	166	53
	104	88	82

E.C.G. - Acute antero-septal infarct. Evolution on the 12th day.

R.L. (M. 51 years). (Casesheet 175084).

Admitted 21.12.61. Discharged 21.1.62.

Complained of severe precordial pain on the morning of admission which wakened him from sleep and persisted for four hours.
Previous history of myocardial infarction five years ago.

On admission no evidence of shock, cardiac decompensation or cyanosis. B.P. 130/95 mm.Hg. Pulse 80 per minute, regular and of good volume. Heart is not enlarged to clinical examination. The heart sounds are of poor quality, particularly the first sound which is scarcely heard. No friction present.

Progress - Recurrent episodes of chest pain with the subsequent development of presystolic triple rhythm over the first two weeks. Thereafter convalescence uneventful.

Serum Transaminase -

	Day 2	Day 3	Day 5
S.G.O.T.	23	27	72
S.G.P.T.	25	33	39

E.C.G. - initial ischaemic change developing into posterior infarct. Cardiogram evolved sixth day.

S.N. (M. 65 years). (Casesheet 156272).

Admitted 28.11.61. Discharged 2.1.62 .

Admitted because of recurrent severe attacks of chest pain radiating to his neck and left arm 48 hours earlier.
Previous history of acute myocardial infarction eight months ago.

On admission not shocked. No evidence of cardiac decompensation. No cyanosis. B.P. 120/70 mm.Hg. Heart sounds normal, pulse 80 per minute, regular and of good volume.

Progress - two further episodes of chest pain after admission without deterioration in the clinical or electrocardiographic state. Treated with anticoagulant therapy.

Serum transaminase:

	Day 1	Day 2	Day 6
S.G.O.T.	141	284	21
S.G.P.T.	210	380	6

E.C.G. - Subendocardial lateral infarct. Evolution at fourteen days.

E.T. (M. 44 years). (Casesheet 157565).

Admitted 1.6.61. Discharged 13.7.61.

On admission complained of severe chest pain of three hours duration.

Previous history of myocardial infarction on two occasions in three years.

On admission there is no evidence of shock, cardiac decompensation or cyanosis.

B.P. 100/60 mm.Hg. Pulse 80 per minute, regular and of good volume. Heart sounds are normal.

No basal crepitations and no abnormality in other systems.

Progress - Pericardial friction rub was heard on the second day.

Otherwise findings remain unchanged throughout convalescence. Anticoagulant therapy with Warfarin given.

Serum Transaminase:

	Day 1	Day 3
S.G.O.T.	42	50
S.G.P.T.	42	51

E.C.G. - Subendocardial posterior infarct. No change after tenth day.

M.B. (F., 58 years). (Casesheet 173595).

Admitted 28.11.61. discharged 19.1.62.

Complained of severe chest pain radiating down both arms of 48 hours duration. She has vomited several times during this period.

Gives a history of anginal symptoms for six months.

No other cardio-vascular disease.

On admission anxious and restless but not shocked and there is no evidence of cardiac decompensation.

B.P. 145/75 mm.Hg. Pulse 85 per minute, regular and of good volume.

The heart sounds are well heard and there is splitting of the first sound at the mitral area.

No pericardial friction is audible. There are no adventitious sounds at the lung bases.

Other systems are normal.

Progress - Three subsequent attacks of chest pain during her stay in hospital were relieved by vasodilator drugs and did not result in alteration of the cardiogram.

Anticoagulant therapy given throughout without incident.

Serum Transaminase:

	Day 1	Day 3.
S.G.O.T.	63	5
S.G.P.T.	25	17

E.C.G. - Acute posterior infarction. Evolved 13 days.

A.S. (M. 56 years). (Casesheet 173403).

Admitted 26.11.61. Died 28.11.61.

Complained of sudden severe chest pain with sweating and breathlessness of several hours duration.
No previous history of cardio-vascular disease.

On admission pale and shocked with cold clammy extremities. No jugular venous congestion and no evidence of cardiac decompensation.
B.P. 80/60 mm.Hg. Pulse 90 per minute and irregular.
Heart sounds very faint but seem pure. No crepitations at the lung bases.
Other systems normal.

Progress - Initial improvement for 24 hours followed by a further collapse with hypotension from which he could not be resuscitated.

Serum Transaminase:

	Day 1
S.G.O.T.	520
S.G.P.T.	105

E.C.G. - Acute posterior infarct. Not evolved.

I.B. (M. 40 years). (Casesheet 174964).

ADmitted 19.12.61. Discharged 17.1.62.

On admission complained of sudden onset of severe chest pain during exertion lasting half an hour and recurring an hour later. During the past 12 months he has had mild anginal symptoms resulting in some reduction in the exercise tolerance.

On admission there is no evidence of shock or cardiac failure.
B.P. 130/75 mm.Hg. Pulse 65 per minute, regular and of good volume.
The heart sounds are well heard and pure but the first sound is of low intensity. No pericardial friction audible. The lung bases are clear and other systems are normal.

Progress - Without incident during the five weeks stay in hospital.

Serum Transaminase -

	Day 2	Day 3	Day 4
S.G.O.T.	138	105	57
S.G.P.T.	42	45	25

E.C.G. - Acute antero-septal infarction. Evolution in 20 days.

S. K. (F. 41 years). (Casesheet 158608).

Admitted 11.6.61. Died 11.6.61.

History of angina of one year's duration. Developed severe constant retro-sternal pain radiating down the left arm at 6 p.m. on the night of admission which persisted until admission.

On admission she was breathless and slightly shocked with pallor and a pulse of 100 per minute, the skin being cool and clammy.
B.P. 135/95 mm.Hg. Pulse was regular but of low tension and amplitude.
The heart sounds are both audible and there is an apical systolic murmur.

Progress - Shortly after admission she became severely shocked with orthopnoea and pulmonary oedema and remained so until her death.

Serum Transaminase:

Not obtained.

E.C.G. - Minimal changes more in keeping with ischaemia than infarct.

Post-Mortem - This shows the anterior descending branch of the left coronary artery occluded 15 mm. from its origin as the cause of infarction.

A.D. (M. 57 years). (Casesheet 175489).

Admitted 29.12.61. Died 12.1.62.

On admission complained of severe chest pain of one hour's duration relieved by an injection of Morphine. Gives a history of increasing angina over the preceding four weeks.

On admission is pale, anxious and sweating. There is marked jugular venous congestion and a trace of sacral and ankle oedema is present.
B.P. 160/100 mm.Hg. Pulse 90 per minute and regular.
The heart sounds are well heard with muffling of the first sound.
There is no murmur or pericardial friction. There are bilateral basal crepitations on auscultation of the lungs.
Other systems are normal.

Progress - Pericardial friction audible on the 2nd day after which satisfactory recovery appeared to be taking place. Sudden death occurred on the fifteenth day.

Serum Transaminase:

	Day 2	Day 3	Day 4	Day 5.
S.G.O.T.	83	136	82	21
S.G.P.T.	70	96	61	33

E.C.G. - Acute anterior infarction. Cardiogram not evolved.

J.S. (M. 51 years). (Casesheet 172759).

Admitted 19.11.61. Died 20.11.61.

On admission complained of intermittent angina for two years since a previous infarction. Had an exacerbation of angina for one week culminating in a severe attack of pain on the afternoon of admission associated with breathlessness and sweating and not relieved by an injection of Morphine.

On admission a pale, shocked, ill-looking man with jugular venous congestion and cyanosis.
B.P. 110/90 mm.Hg. Pulse 90 per minute , of poor volume.
The heart sounds scarcely audible but no obvious murmur or friction.
Crepitations present at both bases.

Progress - Condition remained grave and he died within 12 hours of admission.

Serum Transaminase:

	Day 1.
S.G.O.T.	280
S.G.P.T.	61

E.C.G. - Acute antero-septal infarct. Not evolved.

S.B. (M. 65 years). (Casesheet 152560).

Admitted 11.1.62. Discharged 14.2.62.

On admission he complained of severe chest pain which started while in bed and persisted for several hours. During this time he became severely breathless. He was actually on anticoagulant therapy as a long-term measure because of a previous history of myocardial infarction.

On admission he appeared mildly shocked. There was no evidence of cardiac failure.
B.P. 100/60 mm.Hg. Pulse 84 per minute and regular.
The heart sounds were obscured by a widespread pericardial friction rub.
Crepitations present at both bases.

E.C.G. was difficult to evaluate in view of his previous episodes but he appeared to have sustained a lateral extension of a former antero-septal infarct.

Serum Transaminase:

	Day 2	Day 5
S.G.O.T.	115	27
S.G.P.T.	55	28

Progress - Intermittent pericardial friction persisted for three weeks. Evidence of congestive cardiac failure present with oedema and hepatomegaly

but responded to diuretic therapy. In the third week he developed a respiratory infection which was treated with Chloramphenicol. In addition anticoagulant therapy was given for four weeks and then withdrawn.

He has been discharged to continue with diuretic therapy alone.

GROUP C.

PLEASE REFER TO TABLE C; I - V. Ch. 7.

APPENDIX III

CASE HISTORIES - HEART BLOCK SERIES.

GROUP D.

E.

F.

G.

GROUP D.

A.F. (M.65 years).

Admitted with recurrent Stokes-Adams attacks of sudden onset over a period of 48 hours. Previous history of myocardial infarction five years ago.

On admission no evidence of shock or congestive cardiac failure was present.

Pulse rate was 40 per minute; B.P. 140/60 mm.Hg.

No abnormality was found in other systems.

E.C.G. showed complete heart block with evidence of posterior infarct.

Progress - Treated with ephedrine, grs. $\frac{1}{2}$, four times daily for four days during which time the pulse rate remained unaltered and the number of Stokes-Adams attacks continued at about five per day. Started on oral prednisolone, 30 mgms, daily. No further Stokes-Adams attacks occurred after the first 12 hours of therapy and within 36 hours the cardiogram had reverted to sinus rhythm and remained so when prednisolone therapy was withdrawn over two weeks.

This patient remains well and fully active to the present date.

M.F. (F. 60 years). (Casesheet 157019).

Admitted 7.2.61. Discharged 17.3.61.

On admission was not shocked and showed no evidence of cardiac failure.

She is obese and heart sounds are poorly heard.

B.P. 110/80 mm.Hg. Pulse 78 per minute, poor volume. No crepitations at the lung bases and other systems normal.

E.C.G. showed an acute posterior infarct with Wenckebach type A rhythm.

Progress - She was observed for 48 hours during which her condition deteriorated slowly and frank A-V dissociation appeared with signs of an extensive anterior infarct.

Prednisolone, 30 mgms daily, was started and sinus rhythm was obtained six days later. Thereafter the steroid dose was gradually reduced without incident and she was discharged from hospital to continue with long-term anticoagulant therapy.

R.T. (M. 68 years). (Casesheet 138302).

Admitted 7.12.60. Discharged 12.1.61.

Admitted with severe chest pain of four hours duration. No previous history of cardio-vascular disease.

On admission appeared ill, pale clammy skin, but no cyanosis or oedema. B.P. 110/60 mm.Hg. Pulse 40 per minute.

E.C.G. showed complete heart block with a ventricular rate of 38 per minute.

Progress - Treated with dexamethazone, 2 mgms, q.i.d. On the 5th day he now seemed to have a latent heart block and on the 6th day he was in sinus rhythm.

He was discharged well after a slightly prolonged convalescence, the steroid therapy being discontinued before discharge.

J.T. (M. 78 years). (Casesheet 133336).

Admitted 19.2.60. Discharged 21.3.60.

Admitted with a complaint of severe chest pain over three days of gradually increasing severity. Vomiting on day of admission.

On admission orthopnoeic with marked jugular venous congestion. The heart sounds are poorly heard.
B.P. 115/55 mm.Hg. Pulse rate 35 per minute and regular.
Crepitations were heard at both bases.
Other systems normal.

E.C.G. showed posterior infarct with complete heart block.

Progress - He was treated with bedrest and prednisolone. Rhythm had improved to latent heart block on 4th day and showed sinus rhythm on the 14th day. The pulse rate had been noted to rise to normal some days prior to this record.

A.H. (M. 61 years). (Casesheet 138897).

Admitted 11.1.61. Died 5.2.61.

Complained of severe breathlessness on exertion, increasing over 5 years. Had noticed tightness in his chest on walking for several days prior to admission.

On admission distressed, orthopnoeic; ankle and sacral oedema.
Marked cyanosis.
B.P. 140/100 mm.Hg. Pulse was 80 per minute.
Heart sounds were well heard and there were no murmurs. Bilateral basal crepitations were heard and the liver was palpable at one finger breadth below the costal margin.

E.C.G. - The initial cardiogrm showed an acute antero-septal infarct with a supra-ventricular tachycardia.

Progress - Treatment was started with Digoxin and then Procaine Amide, ½ gm. intravenously. The following day the cardiogram showed complete heart block after 24 hours Procaine Amide during which time there had been no improvement. The dose was reduced and a further episode of ventricular tachycardia supervened. Dexamethazone was also started in a dose of 2 mgms, q.i.d. and other drugs were gradually withdrawn.

Sinus rhythm was restored after two weeks during the reduction of steroids. A Wenckebach Type A record was obtained on the last day of treatment.

It was intended to increase his dose, but he died suddenly that evening.

J.A. (M. 63 years). (Casesheet 136752).

Admitted 17.1.60. Died 20.1.60.

On admission complained of severe retro-sternal pain of 3 hours duration associated with sweating and dyspnoea.

On admission he was pale but apart from slight jugular venous congestion and a one finger breadth liver there was no evidence of cardiac embarrassment.
B.P. 130/70 mm.Hg. Pulse 72 per minute.
The heart sounds were obscured by a pericardiac friction rub.
There were no basal crepitations.

Serum Transaminase:

	Day 1.
S.G.O.T.	110
S.G.P.T.	27

E.C.G. - On admission showed an aucte antero-septal infarct with multiple extrasystoles. The following day the cardiogram showed a complete heart block.

Progress - Dexamethazone, 2 mgms, q.i.d. was started but no response had been achieved prior to his death the following morning.

D.U. (M. 63 years). (Casesheet 136475).

Admitted 22.8.60. Died 8.9.60.

On admission complained of severe chest pain and two episodes of loss of consciousness both of short duration.
Has had chronic bronchitis for 30 years.

On admission he appeared shocked and was considerably distressed.
No cyanosis and no oedema but the liver was enlarged three finger breadths below the costal margin.
B.P. 105/85 mm.Hg. Pulse 66 per minute and irregular. Heart sounds distant but seemed pure.
Crepitations at both bases.

E.C.G. - Initial cardiogram showed complete heart block.

Progress - Treated with prednisolone, 5 mgms, q.i.d. Latent heart block present on 8th day. Sinus rhythm present on the 9th day. An extensive posterior infarct was revealed. His progress appeared to be satisfactory until 17th day, when after a severe melaena he collapsed and despite transfusion died shortly after. There was no known history of ulcer.

GROUP E.

J.S. (M. 58 years). (Casesheet 151276).

Admitted 31.1.61. Discharged 2.3.61.

Admitted profusely collapsed with story of severe chest pain and collapse 12 hours previously.

No previous history of cardio-vascular disease.

On admission there was cyanosis, jugular venous overfilling, crepitations at both lung bases.

B.P. unrecordable. Pulse 14 per minute and regular.

Only occasional muffled sounds were heard over the precordium.

Frequent Stokes-Adams attacks occurring.

E.C.G. - Complete heart block, 14 per minute.

Progress - Given 100 mgms Hydrocortisone intranveously.

Sinus rhythm restored 53 minutes later. During the ensuing 24 hours varying degrees of block from complete to 3 - 1 recorded when steroid therapy was withdrawn or reduced only to respond within thirty minutes each time when a fresh supplement of hydrocortisone was injected.

Day 2 - Cardiogram shows sinus rhythm with left bundle-branch block.

Day 9 - Left bundle-branch block no longer present. Antero-septal infarct now evolving. Posterior leads remain normal.

Subsequent progress was uneventful and no further Stokes-Adams attacks occurred.

Anticoagulant therapy was given during admission and continued on discharge.

D.A. (M. 61 years). (Casesheet 153376).

Admitted 25.4.61. Discharged 30.6.61.

Admitted still having severe retro-sternal pain which had lasted three hours.
No previous history of cardio-vascular disease.

On admission pale and shocked looking. No evidence of cardiac decompensation.
B.P. 105/60 mm.Hg. Pulse 40 per minute.
Heart sounds muffled, the first sound particularly being very soft.
No basal crepitations and no abnormality in other systems.

Serum Transaminase:

	Day 1	Day 2	Day 4	Day 5
S.G.O.T.	66	135	50	27
S.G.P.T.	102	150	66	55

E.C.G. showed posterior myocardial infarction with complete heart block.

Progress - 100 mgms Hydrocortisone given intravenously. Progressive reduction in the degree of block observed over the next 90 minutes. Sinus rhythm restored after 78 minutes. Slow infusion containing Hydrocortisone continued for 12 hours. E.C.G. after 12 hours appears normal. Changes of posterior infarction recurred during withdrawal of steroids. Convalescence uneventful with anticoagulant therapy continued after discharge.

J.S. (M. 72 years). (Casesheet 163371).

Admitted on 20.7.61. Died 22.7.61.

Complained of increasing breathlessness on exertion of three months duration. There had been a sudden deterioration in exercise tolerance with severe dyspnoea ten days prior to admission.

On admission he was grossly dyspnoeic with cyanosis, sacral and ankle oedema and jugular venous congestion.
B.P. 120/80 mm.Hg. Pulse 60 per minute and regular.
Both heart sounds were present and seemed pure. No auricular sounds were heard. There were rales at both bases and the liver edge was palpable four finger breadths below the costal margin.

E.C.G. - Recent anterior myocardial infarction and an old posterior infarct.

Progress - Despite treatment with Hydrocortisone during the 24 hours after admission he died with heart block unrelieved.

Post-mortem showed a massive anterior infarct, recent in nature together with an older infarct involving the septum and presumably the conducting tissue.

A.M. (M. 46 years). (Casesheet 176560).

Admitted 19.9.61. Discharged 19.10.61.

Complained of continuous pain radiating between shoulder blades and into both arms. The pain came on while walking. There was no previous chest pain or cardio-vascular illness.

On admission was distressed and in severe pain with moderate shock and slight cyanosis.

B.P. 125/100 mm.Hg. Pulse 110 per minute.

Heart sounds scarcely audible. No pericardial friction.

No basal crepitations.

No abnormality in other systems.

Serum Transaminase:

	Day 1	Day 6
S.G.O.T.	73	40
S.G.P.T.	54	57

E.C.G. On admission showed a right bundle-branch block with antero-septal infarct.

Progress - Started on hydrocortisone regime. On third day collapsed and showed severe shock. Cardiogram showed complete heart block with auricular fibrillation. Intravenous hydrocortisone started and within an hour the fibrillation was gone, but the heart block picture remained. 600 mgms Hydrocortisone given throughout the next 12 hours. Sinus rhythm restored

within 12 hours but right bundle-branch block persists. Bundle-branch block gone eight days later during the prednisolone regime and did not recur.

Discharged well to continue anticoagulant therapy.

J. McF. (M. 63 years). (Casesheet 168357).

Admitted 28.9.61. Died 8.10.61.

Admitted with complete heart block having had an episode of pain in the left shoulder and arm at home the previous day.
Had previously been hypertensive and had a past history of pericarditis five years ago.

On admission he was breathless and slightly cyanosed. There was no evidence of oedema or hepatomegaly but basal crepitations were audible.
He was not shocked.
B.P. 110/80 mm.Hg. Pulse 60 per minute with varying periods of complete and 2 - 1 heart block shown on the E.C.G. Heart sounds were normal.

E.C.G. - In addition to block, cardiogram showed evidence of acute posterior infarction which was not evolved at the time of death.

Progress - 100 mgms Hydrocortisone given initially and followed by intravenous dextrose drip into which a total of 700 mgms Hydrocortisone was given in 24 hours. Sinus rhythm was restored 21 hours after steroid therapy was started. During this period oliguria was apparent and evidence of fluid overload was observed. The face was puffy, slightly oedematous and there was jugular venous congestion. The liver edge was not palpable, but this was partly due to an obese abdomen. The urinary output was nil on the second day and 4 ozs. on the third day and during this time the blood urea rose from an initial level of 55 to 230.
On the fourth day the output was 21 ozs. and thereafter an increasing diuresis

resulted in a general improvement in the condition and a gradual fall in the blood urea. The normal regime of steroids and anticoagulant was followed and his death was unexpected and the result of a mesenteric embolism on the tenth day.

Post-mortem - The cardiac changes are discussed in detail in the text. There was infarction of the distal half of the jejunum and two-thirds of ileum. In the kidneys many glomeruli were hyalinised with an increase in interstitial fibrous tissue - in keeping with mild hypertension.

A.W. (M. 71 years). (Casesheet 167729).

Admitted 21.9.61. Discharged 25.11.61.

Admitted to the ward with pernicious anaemia which was under treatment. Had a previous history of a mild coronary thrombosis one year previously. Collapsed suddenly in the ward and appeared to have died.
No pulse, no heart sounds and respiration ceased.

An E.C.G. taken immediately showed ventricular fibrillation and cardiac resuscitation was performed by external cardiac massage followed by thoracocotmy, internal massage and electrical defibrillation. Following the shock an idio-ventricular rhythm was obtained.
Hydrocortisone was given immediately intravenously, and over the next 30 minutes there was a progressive improvement in the cardiogram through all stages of complete block to partial block, latent block and sinus rhythm. An acute posterior infarct was disclosed thereafter.

Progress - Steroid therapy was continued with standard regime and sinus rhythm was maintained throughout. The patient was discharged well after a slightly prolonged convalescence.

L.F. (M. 56 years). (Casesheet 174636).

Admitted 13.12.61. Discharged 31.1.62.

Complained on admission of severe pain and tightness across the chest two days prior to admission lasting one hour. On the day before admission he had a similar pain lasting six hours.
Breathlessness on exertion had occurred in the past month.

On admission he was not shocked. There was no venous engorgement in the neck and no oedema, but he was slightly cyanosed and the liver was enlarged four finger breadths.
B.P. 110/80 mm.Hg. Pulse 80 per minute and regular.
Heart sounds were obscured by a widespread pericardial rub.
He was markedly dyspnoea at rest.

Serum Transaminase:

	Day 2	Day 14
S.G.O.T.	130	28
S.G.P.T.	169	40

E.C.G. - The initial cardiogram showed RT elevation in the posterior leads suggesting myocardial injury but not frank infarct. The P-R interval on this record is normal. Four days later the cardiogram showed 3 - 2 heart block and there had been a general deterioration with gross congestive cardiac failure.

Progress - Four hours after intravenous steroid therapy started, the cardiogram showed latent heart block (P-R = 0.24 secs.) completely regular. Thirty minutes later after another 50 mgms Hydrocortisone, the cardiogram showed a P-R interval of 0.2 - 0.22 secs. The routine steroid course was continued thereafter.

One week after stopping steroids he had a cerebral vascular episode with collapse and steroids were restarted. At this point he was in severe congestive cardiac failure despite therapy with Mersalyl and Chlorothiazide. During the second course of steroids the urinary output increased from an average of 30 ozs. per day to around 50 ozs. per day and the failure decreased progressively. The P-R interval remained normal after the initial return to sinus rhythm.

A.K. (M. 65 years). (Casesheet 174994).

Admitted 20.12.61. Discharged 20.1.62.

Admitted with a complaint of rapidly increasing breathlessness on exertion for ten days. During this time he has had a burning sensation in the epigastrium and lower chest with an inconstant relation to exertion.
Has been treated for hypertension for six months.
Has a past history of tuberculous chest infection.

On admission distressed and dyspnoeic with sacral and ankle oedema and marked jugular venous congestion.
B.P. 200/110 mm.Hg. Pulse 100 per minute and irregular due to frequent extrasystoles.
Enlargement to the left - apex beat sixth left interspace; $5\frac{1}{2}$".
Heart sounds are pure. There are crepitations at both lung bases.
The liver is not palpable and the other systems are normal.

Serum transaminase:

	Day 2	Day 3	Day 4
S.G.O.T.	34	27	28
S.G.P.T.	18	18	18

E.C.G. - Antero-septal infarct of indeterminate age. Serial cardiograms show increasing T inversion in V1-V4 consistent with recent injury.

Progress - On 7th day collapsed suddenly with an unrecordable B.P. Pulse 60 per minute. E.C.G. showed complete heart block.

Given intravenous hydrocortisone, 100 mgms, 20 minutes after collapse and repeated two hours later and again at four hours.

Sinus rhythm re-established within four hours.

Total hydrocortisone given 500 mgms in 24 hours.

D.M. (M. 62 years).

On admission complained of severe central chest pain of 22 hours duration. Similar episode one month previously but no real effort angina.

On admission he was shocked and had cyanosis of the lips and ears. There was jugular venous congestion and bilateral basal crepitations present.
B.P. 90/60 mm.Hg. Pulse 60 per minute and regular. Heart sounds poorly heard but seemed pure.

E.C.G. - Complete heart block with right bundle-branch block.

Progress - Given 300 mgms hydrocortisone over 24 hours during which time the complete block and then the right bundle-branch block had disappeared. At the time of writing he remains well; continuing anticoagulant therapy.

GROUP F.

A.T. (F. 83 years).

Admitted because of attacks of loss of consciousness of increasing frequency over 4 weeks. No definite evidence of coronary artery disease from the previous history.

On admission she is an elderly but well nourished woman with no evidence of congestive cardiac failure;
B.P. 180/70 mm.Hg. with a collapsing pulse, rate 38 per minute and regular. There is a loud to-and-fro murmur and thrill
at the aortic area and in the carotid vessels.

E.C.G. shows complete heart block with no evidence of recent infarction.

Progress - Prednisolone, 30 mgms, per day given for 48 hours without effect and withdrawn thereafter in case congestive cardiac failure should be added to the problem.

J.H. (M. 47 years). (Casesheet 151536).

Admitted 26.1.61. Discharged 9.3.61.

Admitted for investigation of effort dyspnoea and syncopal attacks of two years duration.

On admission a wellbuilt fit looking man with no oedema, no cyanosis and no clubbing of the fingers.
B.P. 110/90 mm. Hg. Pulse 60 per minute and regular.
The apex beat was forceful and left ventricular in type and fell outwith the mid clavicular line. There was splitting of the second sound at the base and a systolic murmur of the ejection type heard over the aortic area and conducted into the neck.

E.C.G. - Left bundle-branch block and latent heart block. At intervals periods of complete heart block occurred during his admission.

Progress - A trial of intravenous hydrocortisone given over a period of 12 hours during a phase of latent heart block did not restore sinus rhythm, nor did it appear to shorten the P-R interval to any extent. A diagnosis of aortic stenosis was confirmed by X-ray and cardiac catheterisation.
He had been discharged from hospital awaiting surgical procedure.
Latent heart block persists.

E.S. (F. 49 years).

Admitted for investigation of repeated attacks of loss of consciousness for which a diagnosis of epilepsy had been tendered.

On admission no obvious neurological findings were detected and the cardio-vascular system was normal to clinical examination.

Progress - Lumbar puncture and radiological examination revealed no abnormality in the central nervous system. An E.C.G. showed latent heart block with a P-R interval of 0.28 sec. This was unaltered in two weeks treatment with Ephedrine. An occasional minor Stokes-Adams attack recurred during this time. On 30 mgms Prednisolone daily. No further attacks occurred. The P-R shortened progressively over one week to 0.24 sec. No further reduction was achieved and this increased again on attempting withdrawal of therapy. A maintenance level of 10 mgms daily was continued for this reason.

E.Y. (M. 63 years).

This patient who had a history of a previous myocardial infarction was found to have a latent heart block.

Progress - Since there was no other complicating factor such as digitalis therapy or electrolyte upset, a trial of prednisolone, 30 mgms, daily for two weeks was instituted.

The cardiographic change was reviewed at the end of this time and showed no appreciable difference in the P-R interval. Grade I heart block persisted.

Therapy was discontinued at this point as there were no Stokes-Adams attacks and the patient was symptom free.

J.Y. (M. 64 years).

Admitted with left heart failure having had a previous posterior infarction two months earlier while on holiday.

E.C.G. showed a latent heart block associated with old posterior infarct.

Progress - Diuretic therapy was used in the first instance but only the pulmonary congestion was relieved.
Thereafter prednisolone, 30 mgms, daily was tried for two weeks to observe the effect on the P-R interval.
No appreciable change occurred and the reading of 0.24 - 0.26 sec. persisted.

A.C. (M. 71 years). (Casesheet 163640).

Admitted 5.8.61. Discharged 5.9.61.

Admitted because of recurrent Stokes-Adams attacks with loss of consciousness. These have been occurring with increasing frequency for 8 months. No definite history of myocardial infarction previously.

On admission no evidence of shock or congestive cardiac failure was present. Pulse 54 per minute, irregular. The heart does not seem enlarged to clinical examination and the heart sounds were normal.
B.P. 180/70 mm.Hg.

E.C.G. showed an irregular ventricular rate of 54 per minute with a partial right bundle-rbanch block.

Progress - Treated with ephedrine in doses of 2 grs. daily without benefit. After 10 days prednisolone, 30 mgms, daily was instituted. Stokes-Adams attacks stopped within 48 hours and did not recur. Ventricular rate showed a progressive rise from 50 per minute to 100 per minute with auricular fibrillation. Thereafter the dose of Prednisolone has been gradually reduced. During reduction the ventricular rate has fallen progressively and at a maintenance level of 5 mgms daily he remained well with no Stokes-Adams attacks and a ventricular rate of 60 per minute.

GROUP G.

A.B. (M. 49 years). (Case sheet 59847).

Admitted 13.3.56. Discharge 13.4.56.

Was admitted to hospital three days after an acute myocardial infarction. Cardiogram done on the day of infarct showed complete heart block with a transmural posterior infarct.

On admission there was no evidence of shock or congestive cardiac failure. Complete heart block was still present with a pulse rate of 44 per minute. B.P. 110/80 mm.Hg.
There was no abnormality in the other systems.

Progress - Two days after admission (5th day) cardiogram showed 2-1 block. On the 7th day of admission (10th day) the cardiogram showed a latent heart block which resolved to sinus rhythm on the 16th day of the illness.
His convalescence was uneventful. Anticoagulant therapy was given throughout.

J.S. (M. 76 years). (Casesheet 136955).

Admitted 20.9.60. Died 22.9.60.

Admitted with severe chest pain radiating into his left arm of several hours duration.
History of anginal discomfort on exertion for nine hours with a probable infarct at the outset.

On admission severely collapsed with pallor, peripheral failure and cyanosis.
B.P. 84/50 mm.Hg. Pulse 42 per minute and regular.
Heart sounds almost inaudible. No murmurs or pericardial friction heard.
Crepitations at both bases. Liver edge was just palpable below the costal margin.

Progress - Resuscitation was attempted with pressor agents and an initial cardiogram was not seen until 21.9.60 at which time it was showing that he had a complete heart block. Despite therapy with pressor agents and adrenaline, there was no improvement in the rhythm before his death 18 hours later.

APPENDIX IV.

STATISTICAL ANALYSES AND

ADDITIONAL TABLES.

APPENDIX

11 a.

EFFECT OF SHOCK ON SURVIVAL.

	A	B	C	Total
Died	5	7	25	37
Survived	8	2	16	26
Total	13	9	41	63

$X^2 = 3.621.$

No significant difference between Groups.

11 b.

EFFECT OF FAILURE ON SURVIVAL.

	A	B	C	Total
Died	6	5	21	32
Survived	5	2	8	15
Total	11	7	29	47

$X^2 = 1.215.$

No significant difference between Groups.

11 c.

EFFECT OF SHOCK AND FAILURE ON SURVIVAL.

	A	B	C	Total
Died	5	5	19	29
Survived	3	1	4	8
Total	8	6	23	37

$X^2 = 1.151.$

No significant difference between groups.

EFFECT OF MAJOR INFARCTS ON SURVIVAL.

	Hydro-cort.	Controls	Survey	Total
Died.	7 (8.28)	5 (4.89)	29 (27.83)	41
Survival	15 (13.72)	8 (8.11)	45 (46.17)	68
Total	22	13	74	109

$X^2 = 0.399.$

Not significant.

EFFECT OF FAILURE ON SURVIVAL.

	Hydro-cort.	Controls	Survey	Total
Died	6 (7.49)	5 (4.77)	21 (19.74)	32
Survived	5 (3.51)	2 (2.23)	8 (9.26)	15
Total	11	7	29	47

$X^2 = 1.215.$

No significance.

APPENDIX 15a.

DISTRIBUTION OF MAJOR INFARCTS WITH PREVIOUS HISTORY.

Group A.	Group B.	Total
13	8	21
2	9	11
15	17	32

$\chi^2 = 3.92$ $P < 0.05$

Test shows that Group A is significantly different from B.

APPENDIX

EFFECT OF SEVERITY ON SURVIVAL.

CASES WITH 3 or 4 FEATURES.

Group A		B	C	Total
Died	6	6	22	34
Survived	4	1	5	10
Total	10	7	27	44

$\chi^2 = 2.400$

No significant difference between the Groups.

P-R INTERVAL. HYDROCORTISONE.

Initial Reading	1 week	Final
0.16	0.15	0.16
0.16	0.16	0.18
0.16	0.12	0.16
0.20	0.16	0.18
0.16	0.13	0.16
0.14	0.14	0.14
0.12	0.14	0.14
0.18	0.16	0.16
0.16	0.13	0.13
0.18	0.16	0.16
0.16	0.16	0.16
0.14	0.14	0.14
0.14	0.12	0.14
0.16	0.14	0.18
0.16	0.16	0.17
0.15	0.15	0.15
0.16	0.15	0.18

P-R INTERVAL. CONTROL.

Initial Reading	1 week	Final
0.18	0.20	0.12
0.16	0.18	0.20
0.16	0.16	0.16
0.18	0.18	0.16
0.16	0.14	0.16
0.16	0.14	0.14
0.18	0.18	0.18
0.14	0.14	0.14
0.16	0.20	
0.16	0.14	0.14
0.16	0.13	0.17
0.15	0.16	0.15
0.16	0.16	0.16
0.18	0.19	0.20
0.12	0.12	o.14
0.14	0.14	0.14
0.12	0.14	0.13
0.16	0.14	0.15
0.18	0.15	0.14

APPENDIX V.

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