Summary

Twelve children with chronic asthma were given a trial course of cortisone and later a trial course of prednisolone, and the results are compared.

The expiratory flow rate (E.F.R.⁴⁰) was used to assess the cases and to measure the response to treatment.

The general effects and relief of symptoms produced by the two drugs were similar, rather more children being rendered symptom-free by prednisolone than by cortisone, on a given dosage.

Seven cases responded better to prednisolone, and two cases responded better to cortisone. The results show that 15 mg. of prednisolone and 75 mg. of cortisone produced a similar satisfactory effect, and on this dosage a peak response was generally observed after two to three weeks. When the dose was reduced, the response usually waned.

The response to adrenaline is at first inhibited and later enhanced during either cortisone or prednisolone therapy.

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USE OF PRESSOR AGENTS IN SHOCK IN MYOCARDIAL INFARCTION

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The mortality from cardiac infarction, substantially reduced in recent years by the widespread use of anti-coagulants, may be capable of still further reduction. There are many patients who develop, at the onset of the attack, a state of shock with low blood pressure. This may be so brief that it has almost passed by the time medical attention is obtained, but when persistent or worsening it has long been recognized as of serious significance. The onset of shock may be delayed for some days, but it is nevertheless of ill omen. When this condition complicates cardiac infarction the mortality rises to about 80% (Selzer, 1952; Gootnick and Knox, 1953; Fink, d'Angio, and Biloon, 1953; Griffith *et al.*, 1954).

Attempts to relieve shock and raise the blood pressure have commonly been unsuccessful, and the wisdom of such attempts has been questioned. Thus plasma and blood transfusions have been ineffective owing to overloading of the circulation and they are now rarely used. The place of digitalis is undecided, although good results have been reported by Gorlin and Robin (1955). Vaso-

pressor drugs used by many investigators have usually been such substances as sympathomimetic amines or their derivatives, including adrenaline, ephedrine, and "paredrine"; all of them produce undesirable effects on the heart itself, such as tachycardia and an increase in the cardiac output and the work of the heart.

The use of pressor agents depends on the assumption that the peripheral vasoconstriction that occurs in the state of shock does not produce a sufficient increase in peripheral resistance. It has been thought that if this peripheral resistance could be further increased a rise of blood pressure would follow and bring about improved circulation to the heart and brain. However, an increase in peripheral resistance alone is not enough to raise the blood pressure; the force of the cardiac contraction itself must be increased in response to the increase in peripheral resistance. It has been found that certain newer amines may possess just such a beneficial direct action on the myocardium. In this paper the results of the use of certain pressor agents in 25 consecutive patients with shock in myocardial infarction are described.

Pressor Agents

Two compounds have been used in the treatment of these patients. They are L-noradrenaline ("levophed") and mephentermine sulphate ("mephine"). The properties and pharmacological and therapeutic effects of these preparations may be outlined as follows.

L-Noradrenaline, the most powerful pressor and general vasoconstrictor agent known, differs from adrenaline in its effects upon the cardiovascular system in some important respects. Unlike adrenaline, L-noradrenaline does not increase the rate or output of the heart. Whereas the total oxygen consumption is raised by 20-30% by adrenaline, it is virtually unaltered by L-noradrenaline. Adrenaline, by its direct effect on the heart, causes a rise in systolic pressure, while the diastolic pressure may fall as a result of the vasodilatation in the large vascular bed of the muscles. L-Noradrenaline, on the other hand, being an overall vasoconstrictor, increases both the systolic and the diastolic pressure. In experiments on dogs Sayen *et al.* (1952) demonstrated that the rise in oxygen tension in the ischaemic zone produced by L-noradrenaline infusion was greater than that caused by inhalation of pure oxygen. Both L-noradrenaline and adrenaline dilate coronary vessels (Burn and Hutcheson, 1949). The pharmacology of L-noradrenaline has been fully reported by von Euler (1955). In fully trained dogs Gazes *et al.* (1953) found that L-noradrenaline increased the contractile force of the heart whereas phenylephrine produced largely pressor effects. They also found that L-noradrenaline gave better results than phenylephrine hydrochloride ("neosynepine") when used to combat shock in patients after myocardial infarction.

Mephentermine sulphate has little or no direct action on the heart muscle and causes no alteration in the heart rate or changes in the electrocardiogram. Although the blood pressure rises owing to an increase in peripheral resistance, cardiac output is not significantly altered. In animal experiments (Hellerstein *et al.*, 1952) in which rotameters within the lumen of the vessels were used it was shown that coronary flow increased as the blood pressure rose; the work of the heart increased very slightly, but the cardiac output remained unchanged. If injections were made at too short intervals the response decreased. Mephentermine is metabolized rapidly and there is no danger of cumulative action. The intravenous dosage varies from 10 to 30 mg., and intramuscularly up to 70 mg., while 15 to 30 mg. can be given at half-hour intervals if necessary.

Method of Use of Pressor Agents

The indication for the use of either of these preparations was simply the existence of shock. While the usual well-

known clinical features of prostration, pallor, sweating, vomiting, coldness of the extremities, and a small thready pulse (not necessarily quick) were present in varying degrees in different cases, the paramount feature of low blood pressure was the one determining the use of L-noradrenaline or mephentermine. If the blood pressure fell below 90 mm. Hg and remained so, particularly if the other signs were impressive, these substances were at once employed. Circumstances particularly calling for their use were abnormalities of rhythm, especially persisting tachycardia, auricular fibrillation, or bradycardia.

If shock was judged to be severe, and if the existing facilities allowed, L-noradrenaline was chosen. It was administered in 5% dextrose or dextrose-saline and not in normal saline, in which it is unstable and deteriorates rapidly. It has been reported by West (1952) that the addition of ascorbic acid to the drip is a further protection against breakdown of the L-noradrenaline, but this substance has not been added to the drip given to any of the patients in the present series. Although skin necrosis did not occur in any of our patients who received L-noradrenaline, it has been reported (Humphreys *et al.*, 1955), and a watch should be kept for a pallor around the vein which would necessitate transferring the drip to an alternative vessel.

An initial concentration of 4 mg. per litre is advised. The drip rate should be adjusted to 60–70 a minute at the start and then doubled after 5 minutes if the blood pressure has not risen by then. The aim should be to maintain a systolic pressure of 100–110 mm. Hg (not more), and the rate of administration of L-noradrenaline should be increased every five minutes, or, alternatively, the concentration doubled until a satisfactory response occurs. Unremitting attention is required both for recording the blood pressure at intervals of two to five minutes and for the frequent adjustments of rate of administration that require to be made in the light of the blood-pressure responses. Cessation of the noradrenaline drip should be slow and cautious.

Mephentermine is suitably employed for shock of less severe degree, or when facilities for intravenous infusions do not exist. Its administration is much simpler, usually by intramuscular injections of 15–30 mg. The intravenous route can be used when a more rapid response is desired, the injection being given slowly from a syringe, taking one or two minutes. If the blood pressure fails to rise within five minutes a further 15–30 mg. may be administered in the same manner. As an alternative, 30 mg. may be added to 500 ml. of 5% glucose and given by intravenous drip, the rate being then altered to maintain the desired response. In addition to the use of a pressor agent all shocked patients were treated by anticoagulant therapy in the conventional manner, starting with heparin and phenindione and continuing with the latter alone.

Of the 25 cases of myocardial infarction complicated by shock which form the basis of the present communication, 12 were treated by mephentermine alone, 11 by L-noradrenaline alone, and 2 by both drugs. Six of these cases have already been included in an earlier report (Shirley Smith and Guz, 1953).

Illustrative Cases

The following seven case reports have been selected as examples of the use and the results of pressor agents in different grades of myocardial infarction with shock of varying degree. In Cases 1 and 2 only L-noradrenaline was used and in Cases 3–5

mephentermine alone. All recovered. The last two cases illustrate the successive use of mephentermine and L-noradrenaline; these patients died in spite of initial response to pressor agents.

Case 1: Severe Posterior Cardiac Infarction with Left Bundle-branch Block and Profound Shock Treated by L-Noradrenaline Infusion with Recovery

A man aged 49 had a third attack of cardiac infarction on March 19, 1954, with severe retrosternal pain, vomiting, and other evidence of shock. Jugular venous congestion was present and the heart was completely irregular at 150 a minute, the pulse being feeble. Cardiac enlargement and pericarditis were present and the blood pressure was not recordable. The cardiogram showed posterior infarction with left bundle-branch block.

Administration of aminophylline and digoxin intravenously brought no result, but within an hour of the start of intravenous infusion of L-noradrenaline the systolic pressure rose to 120 while at the same time the rhythm became regular at 70 a minute (Fig. 1). Infusion of L-noradrenaline was continued for 11 hours in all, and thereafter the blood pressure was maintained steadily at 120/80. An uneventful recovery ensued.

Case 2: Septal Infarction Following Anterior Infarction a Year Earlier. Moderate Grade of Shock and Transient A-V Block. Pressor Response to L-Noradrenaline Followed by Recovery

A fishmonger aged 62 was brought to the casualty department on the night of April 30, 1954, after a syncopal attack. He was conscious and complained only of epigastric discomfort. There was no cyanosis, dyspnoea, or sweating. The apex beat was not palpable. The heart sounds were faint and the blood pressure was 75/50. After an hour or two the pulse had fallen to 38 a minute and the blood

FIG. 1.—Case 1. Severe shock and rapid fibrillation after the onset of a third attack of cardiac infarction. Intravenous infusion of L-noradrenaline was followed at once by restoration of normal pressure and within an hour by conversion to normal rhythm.

pressure to 60/40. Morphine, $\frac{1}{4}$ gr. (16 mg.), and atropine, $\frac{1}{100}$ gr. (0.65 mg.), were given, together with heparin, 12,500 units intramuscularly, and phenindione, 75 mg. An intravenous drip of dextrose-saline containing 4 mg. of L-noradrenaline per litre was begun and run in at approximately 20 drips a minute. Thirty minutes later the blood pressure had risen to 70/50 and the pulse to 50 (Fig. 2). One hour after the start of the infusion the blood pressure

FIG. 2.—Case 2. Profound shock at onset of acute myocardial infarction. Intravenous infusion of L-noradrenaline was followed swiftly by abrupt rise of blood pressure and also by sudden increase in the heart rate.

had reached 100/70 and the pulse 55. The rate of infusion was therefore reduced to 16 drips a minute. The blood pressure was maintained at a satisfactory level and the pulse rate returned to 66. Nine hours from the start the rate of infusion of L-noradrenaline was further reduced to 10 drops a minute, and after 15 hours, when the blood pressure reached 110/70, it was discontinued.

An electrocardiogram on May 3 showed a recent septal infarction and partial A-V block, but the conduction defect had disappeared in a record taken on May 14. The blood pressure ranged from 70/50 to 100/60. Auricular fibrillation occurred transiently for 10 days during convalescence; he was discharged from hospital on June 20.

Case 3: Transmural Antero-lateral Infarction Accompanied by Moderate Shock and A-V Block. Good Response to Mephentermine; Recovery

A research worker aged 54 gave a three-year history of coronary heart disease. On March 30, 1956, he collapsed

FIG. 3.—Case 3. Severe shock accompanying acute cardiac infarction. The graph shows the immediate rise in blood pressure and pulse rate following intravenous injection of 30 mg. of mephentermine.

suddenly with dyspnoea but no pain, and became unconscious briefly. Profuse sweating, pallor, and a blood pressure of 65/40 showed the severe grade of shock. The pulse was regular at 40 a minute. Mephentermine, 30 mg. intramuscularly, was given half an hour after the onset, and this was followed by a rise of blood pressure to 104/70 within half an hour of the injection (Fig. 3). The electrocardiogram showed a transmural antero-lateral infarction of the heart. Gradual recovery followed with signs pointing to aneurysmal bulging of the left ventricle. He was able to return to sedentary work until the time of his sudden death nearly one year after the attack.

Case 4: Posterior Myocardial Infarction with Moderate Grade of Shock and Transient A-V Block. Treated by Mephentermine with Recovery

A man aged 45 was admitted to hospital on March 25, 1956, with severe retrosternal pain lasting two hours; there was sweating and nausea and transient loss of consciousness. The pulse was weak at 50 a minute and the systolic pressure was 80; there was no evidence of congestive failure. The electrocardiogram showed transmural posterior infarction with a P-R interval of 0.3 second. In the course of four hours shock had deepened, with cyanosis, increasing pallor, and lethargy; the pulse fell to 40 a minute, and the blood pressure to 70/30. Mephentermine, 30 mg. intravenously, was given during half an hour, after which time the blood pressure had risen to 110/70. Four hours later the pulse was 70 and cyanosis had disappeared. Twenty-four hours later there was a relapse with further retrosternal pain and a renewed fall of pressure to 70/40. The condition was again retrieved by intramuscular and intravenous injections of mephentermine in the same dosage. During the four following days the clinical state fluctuated greatly with a strong tendency to renewal of shock and severe hypotension.

Mephentermine repeatedly showed a specific pressor effect. There was transient auricular fibrillation at the rate of 60 during a period of hypotension. The phase of recurrent shock and hypotension lasted six days. Normal rhythm was established and the latent heart-block completely cleared up, while the blood pressure remained consistently at 110 systolic during convalescence.

Case 5: Postero-lateral Infarction in a Hypertensive Patient. Delayed Shock of Moderate Grade Responded to Mephentermine. Recovery

A housewife aged 59 with hypertension and coronary disorders had been under treatment for three years. On June 27, 1956, she had severe enduring substernal pain with some evidence of shock. The electrocardiogram showed a large postero-lateral cardiac infarction; the heart was enlarged and gallop rhythm was present. The blood pressure was 170/90. Nineteen hours after the onset further severe pain developed and the blood pressure fell to 90/60. The hypotension was relieved by the intramuscular injection of mephentermine, 15 mg. (Fig. 4). The chart shows subsequent temporary fall of pressure not sufficient to require further pressor treatment. However, three days after the onset there was a further dangerous relapse with the pressure falling to 90/40; this was speedily relieved by further injections of mephentermine, and the patient went on to make a full recovery.

Case 6: Anterior Myocardial Infarction. Severe Shock Failed to Respond to Mephentermine and L-Noradrenaline. Death Ensued

A housewife aged 52 had had angina of effort for five years. Sympathectomy had been performed for hypertension in 1950. She was admitted to hospital on March 1,

1956, with severe gripping retrosternal pain of six hours' duration, vomiting, and sweating. The rhythm was regular at 70 a minute, and the blood pressure was 90/60. An injection of morphine was given and anticoagulant treatment was started. Mephentermine, 30 mg., was given by intramuscular injection. As no improvement was evident an hour

FIG. 4.—Case 5. Shock developing 19 hours after onset of cardiac infarction. Satisfactory pressor effect by 15 mg. of mephentermine given intravenously.

and a half later this dose was repeated, intravenous injection having failed. Nevertheless the pulse rate increased to 160 and the blood pressure remained unaltered with deepening shock and signs of venous congestion developing. In spite of intravenous infusion of L-noradrenaline the blood pressure became unrecordable and remained so until her death six hours later. Necropsy showed thrombosis of the descending branch of the left coronary artery.

Case 7: Extensive Transmural Infarction Postero-laterally in Left Ventricle and a Smaller Infarct Anteriorly. Severe Shock with Congestive Heart Failure. Initial Response to Mephentermine not Maintained, and no Pressor Response to L-Noradrenaline. Death within 24 Hours

A man aged 55 had a five-year history of retrosternal pains radiating to the interscapular region, occurring always 10 minutes after exertion, never during effort. Ten days before admission he was awakened by severe angina, spreading on this occasion to the arms; it persisted for nine hours, accompanied by sweating and nausea. Weakness but no dyspnoea followed the attack. On admission to hospital on February 18, 1956, he was ill and feverish and the pulse was small though regular. The blood pressure was 130/100. There were signs of cardiac enlargement and raised jugular venous pressure with bilateral pulmonary oedema. All peripheral pulses were palpable.

Treatment was started by heparin and phenindione and oral digoxin. On the day after admission he collapsed suddenly with profuse sweating and an unrecordable blood pressure. Mephentermine, 30 mg. intravenously, was given. The blood pressure rose to 125/100, but within three hours had again become unrecordable, with the pulse rate rising to 110. Deepening shock with vomiting and sweating was treated by a further 30 mg. of mephentermine intramuscularly, but in spite of this and the simultaneous starting of infusion of L-noradrenaline death took place half an hour later.

Necropsy showed the heart weight to be 530 g. with hypertrophy of the left ventricle. Transmural infarction was found in the posterior wall of the left ventricle, and the lesion involved the whole of the septum and part of the anterior wall of the left ventricle. Recent thrombosis was present in the anterior descending branch of the left coronary artery and also in the right coronary artery, these vessels being diffusely involved in severe non-calcifying atheroma.

Results and Discussion

Shock due to cardiac infarction differs from surgical shock in certain fundamental respects not yet fully understood. Whereas in surgical shock the heart is healthy and the condition is explained by a diminution of effective circulating blood volume, in myocardial infarction the heart has suffered more or less severe damage and there is no reduction of the circulating blood volume (Boyer, 1944). The initiating factor is the heart itself, the output (mainly of the left ventricle) being reduced owing to a loss of functioning myocardium. Freis *et al.* (1952) found the cardiac output and stroke volume to be reduced, while total peripheral resistance, central venous pressure, and heart rate were increased. The systemic and pulmonary blood volumes were unaltered. However, it has also been found that in some instances there is a widespread vasodilatation in the muscle vascular bed which in the presence of a normal cardiac output results in a fall in blood pressure.

The diminution of coronary blood flow which occurs in shock following myocardial infarction (Corday *et al.*, 1949) impairs further the efficiency of the uninfarcted myocardium and aids in the establishment of a vicious circle whereby low blood pressure reduces coronary flow which still further impairs myocardial contractility, decreasing the stroke volume and the output of the heart. Peripheral vasoconstriction may then occur in an effort to raise the blood pressure sufficiently to improve coronary flow and so halt the process. It is possible that when this does not come about the use of such pressor agents as are here described furthers a process already initiated by the body. To these mechanisms may be added a prolonged circulation time, pulmonary congestion, and a raised venous pressure due to heart failure.

A fundamental fault lies, therefore, in the myocardium. It is important to use a pressor agent whose action does not depend solely on increasing peripheral resistance, for it has been shown that in the presence of a damaged myocardium an increase in peripheral resistance only diminishes still further the cardiac output (Sarnoff *et al.*, 1954). Both mephentermine and L-noradrenaline act directly upon the myocardium to restore the cardiac output; thus with the aid of an increase in peripheral resistance they produce a sustained improvement in the circulation by establishing a satisfactory level of blood pressure.

In the present series of 25 consecutive patients, 12 died. This figure compares favourably with the average mortality of 80% given by most workers for patients who did not receive pressor agents as part of their treatment. On considering the clinical features of our cases certain features emerge for comment.

Previous Cardiac Infarction.—As might be expected, a history of such weighed against recovery. Six of the 12 fatal cases gave a history of previous infarction as compared with three of the survivors.

Duration of shock prior to the institution of treatment often determined the outcome. The average duration of shock in those who survived was 1 hour 40 minutes as compared with five hours in the fatal cases. Gootnick and Knox (1953) concluded that the duration of hypotension was important and that irreversible shock developed during periods of prolonged hypotension; of their 32 cases of severe post-infarction shock, none survived when hypotension persisted over eight hours. Sampson and Zipser (1954) also recorded that duration of shock in their patients who died was twice as long as in those who survived. In the series reported by Griffith *et al.* (1954) 13% of those who had pressor treatment within three hours died, whereas among those in whom shock had existed more than three hours 76% died.

Overfilling of Jugular Veins.—The appraisal of the cervical veins is not easy in shocked patients and time was not spent in making intravenous recordings. However, if the cervical veins were conspicuous other evidence of heart failure was generally present. A raised jugular venous

pressure was found in 8 of the 12 patients who died, but in only 4 of the 13 who recovered. The coexistence of heart failure worsened the outlook for the shocked patient.

Persistent tachycardia was an unreliable guide to prognosis although in general it was unfavourable. It occurred in nine of the fatal cases, but also in six of those who survived.

Bradycardia resulting from partial A-V block occurred in 25% of survivors, but was not seen in those who died. Its occurrence is of limited value, but may perhaps point to a likelihood of recovery. The slow ventricular rate, by allowing both more time for coronary filling during diastole and for myocardial recovery, may conceivably be of benefit to the heart during this critical phase. A-V block may be functional and due to temporary anoxia of the conducting tissue and not to septal infarction. Such functional impairment of conduction has been reported by Lewis *et al.* (1914), who showed how experimentally induced anoxia in cats caused interference with conduction, and they demonstrated that it is the A-V node and the tissues immediately above that are the most susceptible to oxygen lack. In man Greene and Gilbert (1921) showed how a progressive lack of oxygen induces a series of changes in cardiac rhythm and conduction of impulse from auricle to ventricle.

Grade of Pressor Response.—The height to which the blood pressure rises in response to the use of pressor agents is not a reliable guide to whether or not any individual patient is likely to survive. The average rise in blood pressure after the use of one or other pressor agent, or in some cases of both, was 42/33 in those who ultimately succumbed, and 59/35 in those who survived. This lack of relationship was seen in one of the fatal cases, in which the blood pressure rose from an unrecordable level to 125/100 following the administration of mephentermine, while two surviving cases showed rises of only 35/20 (from 60/40 to 95/60 and from 80/60 to 115/80). The most that can be learned from the response is that the higher the rise in diastolic pressure the more likely is the patient to survive, for it is only when an effective diastolic pressure is maintained that adequate coronary circulation is assured to the surviving myocardium.

Prognosis after Recovery from Shock

It has sometimes been held that pressor treatment in the shock of myocardial infarction is of little ultimate value because the remote prognosis remains, in any case, very poor. This is by no means a valid objection, as is shown by the follow-up of those cases previously reported jointly by one of us (Shirley Smith and Guz, 1953). Of their six patients, three survived and were still alive nearly four years after sustaining their original infarction complicated by grave shock.

Two of these have been re-examined and news has been received of the third. Case 2 of the series, aged 71, whose infarction occurred shortly after a major operation in September, 1952, was seen in November, 1956, when she was well and free from pain. Her activity was restricted by osteoarthritis of the hip, but she was not short of breath and showed no signs of failure. The blood pressure was 130/80.

Case 3 of the series, aged 57, had a myocardial infarction in May, 1953. At review in August, 1956, he complained that only in the last four months had he developed some angina on effort and increasing dyspnoea. No signs of heart failure were present. The blood pressure was 140/90.

Case 5 of the series, aged 75, was treated with L-noradrenaline infusion for five hours in April, 1953, when in shock after myocardial infarction. It has not been possible to re-examine this patient, but in March, 1957, her sister wrote to say that she has remained in satisfactory health ever since. Her medical attendant has died, but she has had no occasion to consult his successor.

Summary

The purpose of the present report is to draw attention to the place of pressor agents in the treatment of

shock complicating myocardial infarction. Hitherto myocardial infarction accompanied by severe shock has carried a mortality of 80%. In our consecutive series of 25 cases, only 12 have died. We hold that by the early recognition of the presence of shock and its prompt treatment a number of patients can be saved. That the survivors can lead useful lives free from serious disability for several years is shown by the follow-up of the survivors of the series published by one of us nearly four years ago.

The pressor agents used were L-noradrenaline by intravenous drip infusion, and mephentermine, both intramuscularly and intravenously. Initial treatment of lesser grades of shock should be by intramuscular mephentermine; L-noradrenaline should be used for severe shock and in less severe illness when mephentermine has not been effective. Whereas mephentermine is readily administered as emergency treatment when the patient is first seen, L-noradrenaline requires careful attention to its continuous intravenous administration, thus generally necessitating admission of the patient to hospital.

The duration of shock before treatment is started should be less than two hours if a good result is to be obtained. When shock has been present more than five hours the results of treatment are poor. A raised jugular venous pressure, a history of previous infarction, and a persistent tachycardia are all of ill omen.

An unexpected finding in our series was that bradycardia, even if due to functional A-V block, seemed to indicate a good prognosis.

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"Ergot—the Story of a Parasitic Fungus" is the title of a new film made by the Wellcome Foundation Film Unit. Sir Henry Dale O.M. and Professor Chassar Moir helped with the making of the film, the latter appearing in it to describe the discovery of ergometrine in 1935. The film tells the story of ergot as both a toxic contaminant of rye bread and a valuable medicinal substance. It describes how the complex alkaloids of ergot were isolated and the use to which they are now being put in the treatment of disease and the management of childbirth. Some of the sequences were shot with the help of the obstetric unit of University College Hospital, London. The film (16 mm., colour, with sound track) runs for 27 minutes, and can be borrowed from the Wellcome Film Library, The Wellcome Building, Euston Road, London, N.W.1, free of charge.