Discussion

A patient who is prescribed drugs may take none of them, or he may take them for a short time and then stop, or he may take them irregularly. The answer to the question, "Is this patient taking his drugs?" will depend on the criterion used. A verbal inquiry can compass some or all of the various ways in which a patient may not take his drugs. Urine tests for drug excretion give restricted answers, but have the advantage of objectivity, an advantage of particular importance in this context. In the present study a negative urine test for amphetamine-like substances (including a negative chromatogram where low dosage of chlorpromazine made the first test unsatisfactory) indicates that the patient had not been taking the drug during the previous 24 hours (or longer for imipramine patients according to dose). This might mean only a temporary and isolated lapse in taking his tablets, though sometimes of significant duration. The findings, however, that a second urine test usually gave the same result as the initial one, and that in multiple tests the results from any patient were usually consistent, suggest that a single negative test may generally be taken to indicate that the patient had not been taking his drug at all, or not with any regularity, for many days or weeks.

The use of this criterion has demonstrated a failure rate of 48% in the whole series. This may be compared with failure rates of over 20% (Haler, 1962) and 33–40% (Benstead and Theobald, 1952) in women attending antenatal clinics and prescribed ferrous sulphate. In these studies the failures were apparently assessed as a result of inquiry. In two groups of tuberculous out-patients prescribed P.A.S. urine tests indicated failure rates of 50% (Dixon *et al.*, 1957) and 30–40% (Luntz and Austin, 1960), higher values being related to length of treatment in the latter study. Two reports on schizophrenic out-patients (Parkes *et al.*, 1962; Renton *et al.*, 1963) quote rates of 44–46% obtained by inquiry. Joyce (1962), investigating patients' co-operation in a trial of drugs for rheumatoid arthritis, classified approximately 50% of out-patients as "obedient" on the results of counts of tablets remaining at each interview. He also used a phenol-red marker in the tablets for half the patients, and obtained only 38 of 108 expected positive urine tests; but the significance of this is difficult to judge in the absence of details of the excretion time of the marker. He demonstrated that different conclusions regarding the effects of the drug might be drawn when allowance was made for the varied intake. From these various authors came suggestions that factors relating to failure to take drugs include length of treatment, presence of side-effects, a feeling of well-being, and lack of supervision.

Our findings do little to elucidate the reasons why patients omit their drugs. Age, sex, intelligence, and side-effects had

no apparent influence. The fact that men living alone defaulted more often than those living with their wives suggests a beneficial influence of supervision. The failure rate varied with diagnosis and with the drug, but our observations suggest no simple explanation.

While the causes may remain obscure, the fact seems to be established that a very large proportion of psychiatric out-patients fail to take their drugs. Some consequences of the extent of this failure may be mentioned. There is a considerable waste of drugs and money. The accumulation of unused drugs in the homes of patients is a source of danger. Drug trials in which there is no reliable check on whether the patients are taking the drugs as prescribed can be seriously misleading.

Summary

Tests were made of 125 psychiatric out-patients to ascertain whether they were taking the chlorpromazine or imipramine that had been prescribed.

Criteria of failure to take the drugs were based on information of the drugs' excretion by in-patients, and included both a quantitative test and sensitive and specific chromatographic tests.

The results indicate that the failure rate for the whole series was 48%. The rate for patients prescribed chlorpromazine was slightly higher than that for those prescribed imipramine, and was also higher for depressives than for schizophrenics within the chlorpromazine group.

Failure rate was not associated with age, sex, intelligence, or drug side-effects.

The results are discussed and attention is drawn to the implied waste of drugs, the danger of unused drugs in the home, and the possible unreliability of out-patient drug trials.

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Coarctation of Thoracic Aorta, with Thrombosis of Arch, Treated by Homograft

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Coarctation of the lower thoracic aorta was reviewed by Bahnson, Cooley, and Sloan (1949), and Beattie, Cooke, Paul, and Orbison (1951) were the first to treat a case successfully by resection and the insertion of a homograft.

The following case is reported in view of the mode of presentation, the unique manner of progression at a youthful age, and the successful early treatment.

Case Report

A girl aged 7 years had first been referred to the Hallstrom Institute of Cardiology, Royal Prince Alfred Hospital, from the Royal Newcastle Hospital in July 1962, at the age of 5, when she complained of chest pain that had developed during skipping

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and lasted for 15 minutes. She had been reported to the school medical officer, who made the diagnosis of aortic coarctation.

On admission she was found to have a blood-pressure of 180/140 mm. Hg at rest and large pulsating collateral vessels palpable in the posterior axillary folds; femoral pulses were absent. Indications of left ventricular hypertrophy on the electrocardiogram and the chest radiograph, together with a double aortic indentation on barium-swallow examination, were consistent with an uncomplicated coarctation, and the absence of rib-notching was not considered remarkable.

Thoracotomy was performed in October 1962, when an apparent atresia of the descending thoracic aorta with small intercostal vessels was found (Fig. 1 A). The thoracic aorta was seen to "tail off" sharply at the level of the seventh thoracic vertebra into a heavily scarred string-like obliteration which was densely adherent to the pleura and to the mediastinal tissues for 2½ in. (6.3 cm.). It was then seen to expand again at the level of the eleventh vertebra, where it was joined by two very large intercostal collateral vessels which imparted a marked thrill. The aortic pressure above and below this diseased segment was 200 mm. and 100 mm. Hg, respectively.

It was plain that a graft would be necessary to restore the atretic thoracic-aortic segment. It was decided to defer this operation for some years if possible, since it was more likely to be successful in an older child.

The patient was readmitted two years later on account of breathlessness, recurrent attacks of tonsillitis, adenoiditis, fever, increasing hypertension, and deterioration of her eyesight. On examination the blood-pressure was 220/140 Hg in the right arm. The apex beat was in the sixth intercostal space in the midclavicular line, the femoral pulses were absent, and, as previously, pulsating collateral vessels could be felt in the posterior axillary folds. A loud continuous murmur was heard in the epigastrium. She was found to have grade IV retinopathy. The electrocardiogram showed left ventricular hypertrophy and strain, and a chest film revealed considerable cardiac enlargement. A retrograde aortogram confirmed obliteration of the aorta above the level of the eleventh thoracic vertebra, below which all its branches were of small calibre. The haemoglobin was 12.7 g./100 ml., the E.S.R. 22 mm. in one hour, and the antistreptolysin O titre 625 units. The white-cell count and the blood urea were normal. She ran a continuous pyrexia of 99–100° F. (37.2–37.8° C.), and her pulse rate ranged from 112 to 120.

It was agreed that resection and replacement of the atretic segment of the aorta were necessary to relieve the obstruction and to restore her sight. A synthetic graft was thought less certain to succeed than a fresh arterial homograft, which could be expected to expand somewhat during the years ahead. A graft was therefore prepared consisting of the entire thoracic aorta removed four hours after death under sterile conditions from a 3-year-old child, immediately freeze-dried, and sealed in a vacuum container. The graft was stored for two weeks and reconstituted with heparin-saline before the operation. All adventitia was removed, and the innominate, common carotid, and left subclavian arteries were sutured at their origin in such a way as to minimize kinking as the arch was

opened and the intercostal arteries tied. As the graft was not viable precautions did not have to be taken to ensure growth and prevent rejection.

At thoracotomy on 1 April 1964 the mediastinal tissues were found to be densely scarred around the aorta. The fibrous aortic cord was continuous distally with the blind aorta, into which two large intercostal arteries entered just above the diaphragm, imparting a coarse thrill. Proximally the cord was continuous with aorta occluded by a thrombus which extended into the left subclavian artery (Fig. 1 B). The aorta was divided just distal to the left subclavian artery and the thrombus removed. Although the intima adjacent to the thrombus was greatly thickened, a smooth lumen was obtained by syringing with heparin-saline.

The whole of the aortic graft was used; the proximal end, consisting of the ascending aorta, was sutured in place just beyond the subclavian artery, and the distal end to the aorta just above the diaphragm, in such a manner as to bypass the atretic segment (Fig. 1 C). On releasing the clamps there was little pulsation in the graft, which at first was thought to be thrombosed: this was probably due to back-flow from the intercostal collateral vessels, for good pulsation was soon observed. The graft was sutured to the lung and the chest closed.

Three portions of aorta were examined histologically (Figs. 2, 3, 4). The media was for the most part intact, but it was penetrated from the adventitia by arterioles involved in a vasculitis of varying age and intensity. The walls of some arterioles showed concentric fibrous thickening, while others were frankly necrotic and surrounded by a granulomatous reaction. The venules also showed an acute inflammation of their walls. The affected vessels were surrounded by a dense inflammatory infiltrate of neutrophils, eosinophils, and plasma cells, together with a few small collections of lymphocytes. The intima, which was partly hyalinized and fibrotic, was seen to merge with the fibrin of more recent thrombus, and this fibrotic zone was penetrated by vessels from the media accompanied by inflammatory cells. The general picture was that of a periarteritis with secondary thrombosis and organization.

The patient made a good post-operative recovery. The femoral and posterior tibial pulses returned immediately. The blood-pressure fell to 180/120 mm. Hg within two days and then more gradually to 140/90. Heparin 2,000 units four-hourly was given for six weeks as prophylaxis.

She was readmitted in September 1964 for assessment and aortography. She was well and her sight was normal. The blood-pressure was 135/80 mm. Hg in both arms. The femoral pulses were palpable and not delayed. No collateral vessels were found and the heart had become much smaller. A thoracic angiogram (Fig. 5) showed the left subclavian artery and the thoracic aortic

FIG. 1.—Atresia of aorta with retrograde thrombosis. A: Condition found at thoracotomy in 1962. B: Condition found at thoracotomy in 1964. C: Anatomical appearance after excision and homografting.

FIG. 2.—Transverse section of aorta showing the thickened fibrotic intima and the thrombus occluding the lumen. (H. and E. $\times 10$.)

graft to be patent, with a slight constriction just beyond the curvature but without terminal narrowing.

The patient had grown and become robust since the operation and at the time of writing was active and at the top of her class at school. In February 1965 her visual acuity was found to be 6/9 in both eyes, with normal visual fields, and retinoscopy showed no abnormality apart from definite irregularities of calibre and increased tortuosity of the vessels and unduly pigmented retinæ.

Discussion

The onset of symptoms at the age of 5 years (a period of great activity in childhood), the presence of well-marked collateral vessels, and the finding at operation of very large intercostal vessels joining the blind distal end of the thoracic aorta all suggest either congenital aortic atresia or aortitis acquired during intrauterine or early post-natal life (Bahnson *et al.*, 1949).

FIG. 3.—Aortic wall showing chronic inflammation with vascularization of the media and a granulomatous vasculitis affecting a vessel in the media. (H. and E. $\times 75$.)

FIG. 4.—Chronic inflammation and granulomatous vasculitis in the adventitia. (H. and E. $\times 130$.)

Appreciation of the significant systolic murmur low in the chest and epigastrium, indicative of turbulent flow in collateral vessels, should have aroused suspicion of the condition, which was found at the first thoracotomy and only later confirmed by aortography. An aortogram performed initially would have been invaluable in view of the subsequent course of events.

Mediastinal scarring such as was found at operation does not occur in the common forms of coarctation. The rapid deterioration with evidence of increasing aortic obstruction is

FIG. 5.—Tracing of thoracic angiogram.

attributable to ascending thrombosis in the blind thoracic aorta. Whether the thrombosis was the result of trauma or of arteritis is debatable. The occlusion of vessels arising from the aortic arch has been shown to occur more readily in the presence of a local congenital abnormality (Ross and McKusick, 1953). Such an anatomical abnormality was present in this case, where a thickened aorta ended blindly except for intercostal branches which may or may not have been patent. Trauma could have occurred at exploration. In the Leriche syndrome (Leriche and Morel, 1948) thrombosis starting in diseased vessels at the aortic bifurcation has been observed to extend upwards, progressively obliterating the lumbar and renal arteries, and histology has shown an arteritis similar to that found in the present case. Although the antistreptolysin O titre was raised, there was no convincing evidence of an arteritis secondary to beta-haemolytic streptococcal infection.

The choice of a homograft artery of similar age in preference to a synthetic graft in the case of a young child finds support in the experience of many peripheral vascular surgeons. The vessels of the donor and the recipient can be expected to have similar elastic properties, a particularly important advantage in the case of a very long graft, allowing some degree of passive enlargement *pari passu* with growth. To prevent kinking of the graft opposite the subclavian artery it is necessary to excise an elliptical arterial segment.

Summary

The mode of presentation, progression, and treatment of a young patient with coarctation of the lower thoracic aorta are described.

Increasing disability of a rising diastolic blood-pressure and blurring of the vision due to severe retinopathy were the salient features requiring urgent relief.

This was accomplished successfully by resection and an aortic homograft replacement.

On the basis of the operative findings and of histological examination of the thrombotic aortic sections the aetiology of the lesion was considered to be consistent with vasculitis.

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Phenylbutazone-induced Pericarditis

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The subject of iatrogenic pericarditis was reviewed by Sparer and Davis (1963), and that which follows cardiac surgery has been amply documented. While pneumonectomy is rarely succeeded by pericarditis the post-pericardiotomy syndrome occurs in some 30% of patients in whom a wide pericardial incision has been made (Engle and Ito, 1961). Similarly, pericarditis may ensue subsequent to diagnostic procedures which involve penetration of the pericardium, particularly if blood is effused into the pericardial sac. Therapeutic irradiation of the chest area may result in acute or chronic constrictive pericarditis (Connolly and Burchell, 1961). Only recently has it been realized that pericarditis can be attributable to an untoward reaction of drug medication. The example recorded here is attributed to the administration of phenylbutazone.

Case Report

The patient, a widow aged 64, was known to have osteoarthritis of the cervical spine and of the metacarpal-carpal joints of both thumbs. Because of an exacerbation of the pain phenylbutazone 100 mg. t.d.s. had been prescribed. A week later she developed soreness of the mouth and general malaise and accordingly stopped the treatment. Next day marked and diffuse swelling of the neck and hands appeared and she had a temperature of 100° (37.8° C.). That evening epigastric discomfort, nausea and anorexia, and widespread joint pains were further features. On the following day the joints were swollen and their mobility was considerably restricted, and the urine was noted to be of very dark colour.

On admission to hospital, 15 days from the commencement of phenylbutazone therapy, she was obviously critically ill. Orthopnoea, oedema of the legs, and jaundice were evident. The pulse was rapid and irregular owing to auricular fibrillation, the temperature was 101° F. (38.3° C.), and the respiration rate 30 per minute. The oedema of the neck and hands had to a considerable extent subsided. The apex beat could not be located. Gross pericardial friction was audible over an extensive area of the praecordium. The average B.P. was 120/80. A generalized stomatitis with no ulceration was present, and the liver was enlarged to three fingerbreadths below the costal margin and was tender on palpation.

The results of the special investigations were: Urine, a trace of albumin and heavy concentration of bile. Hb 76% (11 g.). Total W.B.C., 21,300/c.mm. (polymorphonuclears 90%, lymphocytes 9%, mononuclears 1%). Blood urea, 25 mg./100 ml. Paul-Bunnell, no agglutination. Antistreptolysin O titre, 65 units/ml. Serum protein, 5.7 g./100 ml. (albumin 2.6 g., globulin 3.1 g.). Electrophoresis, increase of α 2. Serum G.O.T., 74 S.F. units. Serum G.P.T., 62

S.F. units. Serum lactic dehydrogenase, 580 B.B. units; serum bilirubin, 2.8 mg./100 ml. Thymol turbidity 1 unit. Zinc sulphate turbidity, 3 units. Alkaline phosphatase, 35.3 units. Antinuclear factor absent. Latex fixation test negative. L.E. cells not detected. Serum amylase, 75 Somogyi units. Blood W.R. negative. Virological studies and toxoplasma serology negative. Throat swab culture showed *staphylococcus aureus*. Examination of chest with a portable x-ray apparatus revealed a generalized increase in the cardiac area and venous congestion in the lung fields. The E.C.G. tracing is shown in Fig. 1.

For several days the condition of the patient continued to deteriorate and she was often confused. Digoxin and mersalyl produced no significant change. On her fourth day in hospital prednisone 10 mg. t.d.s. was prescribed. Response to this treatment soon became evident, and six days later normal rhythm was established and the pulse rate fell to 70. Her temperature had by then settled, pericardial friction was no longer detectable, and the dyspnoea and oedema had cleared. The progressive decrease of jaundice was also reflected in the disappearance of bile from the urine and in the pattern of the liver-function tests, the findings of which three weeks from the date of admission were: serum bilirubin, 0.5 mg./100 ml.; thymol turbidity, 1 unit; zinc sulphate turbidity, 4 units; and alkaline phosphatase, 13.1 units. At this time the Hb was 100% (14.6 g.), the W.B.C. 12,900/c.mm., and the E.C.G. tracing showed no significant abnormality (Fig. 2). The patient was fully ambulant, and, apart from persistence of the oral discomfort, symptom-free six weeks from the time when phenylbutazone had originally been prescribed. She has remained well, and when seen three months later the oral symptoms had cleared, physical examination was negative, her E.C.G. had remained normal, and the chest x-ray picture was within normal limits. A cholecystogram revealed a normal appearance and function of the gall-bladder. Prednisone had been tailed off, and she had been without this medication for six weeks with no recrudescence of any of the clinical features.

Discussion

The capacity of a drug to induce pericarditis has been convincingly demonstrated by the observations of Costa, Holland, and Pickren (1961). In a study designed to assess the human pharmacology and antineoplastic value of the purine riboside analogue psicofuranine (6-amino-9-D-psicofuranosyl), three out of four patients treated with this compound developed pericarditis. Necropsy confirmed its presence in the three patients, all of whom were in the stage of advanced neoplastic disease. One patient also manifested pleural inflammatory changes, and it was concluded that psicofuranine had a singular tendency to precipitate inflammatory reactions of serous surfaces. The pericarditis associated with other drugs is, in

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