are neither so severe as to need immediate or permanent insulin nor so mild as to be satisfactorily controlled by dietary restriction alone.

Insulin is indicated in all young and severe diabetics, in diabetics where sepsis or gangrene exists, and, before the days of sulphonylurea therapy, in diabetics who continued to show glycosuria and hyperglycaemia despite adherence to a suitable diet. The initial or hospital dose of insulin in new diabetics is often higher than that subsequently necessary to control the diabetic state. In some diabetics insulin requirements steadily diminish until eventually control is obtained on dietary restriction alone. If these patients are maintained without adequate supervision on the dosage of insulin originally necessary for control, chronic hypoglycaemia may result. This can be particularly disastrous in elderly patients with a cerebral circulation impoverished by arteriosclerotic changes. In elderly patients relapse in the diabetic state can be less dangerous than the daily injection of insulin when the blood sugar is already below normal.

Since the advent of the sulphonylureas, tolbutamide has been used extensively in patients with a mild maturity-onset type of diabetes who have failed to respond to dietary restriction. In conducting trials of oral hypoglycaemic agents it was observed that many newly diagnosed diabetics responsive to tolbutamide did not relapse when therapy was discontinued after six weeks. This routine has been followed subsequently in new diabetics not responding to diet. The diet varied from 1,200 calories in the more obese patients to 2,200 calories in the underweight. The length of observation on diet alone before tablets varied from several months as out-patients in mild obese cases to five days in the ward for severe cases. Although it is always arguable that some of these patients might have eventually attained normoglycaemia after a more restricted diet and prolonged observation, in practice the disadvantages of a short course of tolbutamide are slight so long as proper emphasis is laid on the need for continued dietary restriction. There is evidence in experimental animals that prolonged hyperglycaemia, however produced, can itself cause permanent diabetes, but this can be averted if hyperglycaemia is not sustained (Dohan and Lukens, 1948). If this is true in man, the sooner the blood sugar is restored to normal the better. Patients who relapse when tolbutamide is withdrawn remain responsive to the drug when it is reintroduced, and thereafter treatment can be continuous.

Interval supervision continues to be necessary after insulin or tolbutamide has been discontinued. Good control of the diabetic state requires normoglycaemia or near normoglycaemia, and not merely freedom from symptoms. Hyperglycaemia may carry with it ultimate dangers of degenerative changes in the arteries, kidneys, eyes, and nerves, and these changes have occurred in apparently mild and symptom-free diabetics where hyperglycaemia was allowed to persist. Although it has been shown that remissions may last for many years, relapse may always occur, especially in the face of carelessness in diet or of infection.

Summary

In 550 newly diagnosed diabetics, 184 (33.4%) were adequately controlled by dietary restriction from the start, while a further 145 (26.3%) were ultimately controlled by dietary restriction alone after temporary

treatment with insulin or tolbutamide. The remaining 221 (40.2%) needed permanent insulin or tolbutamide.

The dangers of unnecessary prolongation of insulin therapy are exemplified by two cases of post-hyperglycaemic encephalopathy.

My thanks are due to Miss M. Crowley and her department for the biochemistry results quoted. I am most grateful to Miss G. Weeks for the care she has taken in going through the case records, and to Miss Mason for the preparation of the diagram.

REFERENCES

- Bornstein, J., and Lawrence, R. D. (1951). *Brit. med. J.*, **1**, 732.
Crowley, M. F., Wolff, F. W., and Bloom, A. (1957). *Ibid.*, **2**, 327.
Dohan, F. C., and Lukens, F. D. W. (1948). *Endocrinology*, **42**, 244.
Jones, G. M. (1947). *Amer. J. med. Sci.*, **213**, 206.
Joslin, E. P., Root, H. F., White, P., and Marble, A. (1952). *Treatment of Diabetes Mellitus*, 9th ed., p. 60. Lea and Febiger, Philadelphia.
Wrenshall, G. A., Hartroft, W. S., and Best, C. H. (1954). *Diabetes*, **3**, 444.

ATHEROSCLEROTIC BLOCKAGE IN THE LEFT SUBCLAVIAN ARTERY TREATED BY THROMBO-ENDARTERECTOMY

BY

H. S. SHUCKSMITH, T.D., B.Sc., M.B., F.R.C.S.
Surgeon, General Infirmary and St. James' Hospital, Leeds

Since Takayasu (1908) described blockage of the branches of the aortic arch in Japanese women the condition has been reported as "pulseless disease" (Shimizu and Sano, 1951; Caccamise and Whitman, 1952) and "reversed coarctation" (Frøvig, 1946). The simultaneous blockage of the branches of the aortic arch and of the aortic bifurcation reported by Martorell and Fabré Tersol (1944) is the first record of recognition of occlusion at these two levels in a single patient.

The early papers on Takayasu's syndrome give arteritis, syphilis, and trauma as possible origins of the disease, but later reports suggest that atheroma is the most frequent cause. If this be true, the condition comes into line with the usual pathogenesis of arterial occlusion in other areas. Since the introduction of the technique of aortography by percutaneous puncture of the femoral artery (Seldinger, 1953), demonstration of partial or complete occlusion of one of the branches of the aortic arch is possible before the complete syndrome is established (Wickbom, 1957; Towers *et al.*, 1958).

The basis of this report is atherosclerotic occlusion of the first part of the left subclavian artery in a patient which caused gangrene of the fingers of the left hand and in whom, after confirmation of the site of the block by aortography, thrombo-endarterectomy produced a dramatic improvement in the symptoms and signs.

Case Report

The patient, a woman aged 46, complained of pain in the palm and fingers of the left hand. Examination revealed small areas of fading ecchymoses in the left arm, early gangrenous changes in the left finger-tips (most pronounced in the middle finger), and wasting of the left forearm and small muscles of this hand.

She had had symptoms for 1½–2 years before gangrene of the finger-tips appeared. Small areas of ecchymoses were

first noticed on the left forearm, then round the left elbow, and when gangrene of the finger-tips appeared there were resolving areas of ecchymoses on the left upper arm. The patient experienced tingling of the left fingers over a period of 18 months, and for nine months the fingers had been white and cold first thing in the morning and she had a burning pain in the left palm which lasted some hours. Four months before admission there had been persistent pain in the tips of her fingers, especially the left middle finger, apparently initiated by pressure when the patient was squashed in a football crowd.

The left radial pulse was present but diminished, and there was a thrill and systolic bruit over the left subclavian artery. The oscillometer reading in the right forearm was 4, and in the left 2½. The blood pressure in the right arm was 180/95 mm. Hg and in the left 140/75. The electrocardiogram was normal. Radiographs of the cervical spine showed spondylosis, most marked at the level of the sixth and seventh cervical vertebrae. The Wassermann reaction was negative and the erythrocyte sedimentation reaction 13 mm. in one hour. Aortography by percutaneous puncture of the femoral artery (Dr. P. G. Keates) showed that the left subclavian artery was narrowed for a distance of about 2 cm., starting 2 cm. from its origin, but there was good filling of the axillary, left common carotid, and vertebral arteries (Fig. 1).

Operation

Under general anaesthesia (Dr. D. G. Clark) the patient was placed prone, with the left arm dependent. A periscapular incision enabled the scapula to be mobilized forward and upward, and the fourth rib was then resected. After insertion of rib-spreaders the arch of the aorta and its branches, and the structures in relationship to the under surface of the first rib, were identified across the opened pleural cavity. (Fig. 2.) Pulsation was absent from the first part of the subclavian artery as far as the costocervical branch, and could be felt faintly beyond. A block, which seemed to fill the lumen of the artery, and about 2 cm. in length, was felt from just beyond the origin of the subclavian artery to nearly as far as the costocervicalis. The subclavian artery was dissected free from its origin for 6 cm. After the intravenous administration of 40 mg. of heparin the subclavian artery was clamped, and the block

FIG. 1.—Aortogram showing constriction of the first part of the subclavian artery.

FIG. 2.—View of subclavian artery seen through third interspace.

FIG. 3.—Block removed, 2 cm. long.

FIG. 4.—Block in section.

(Figs. 3 and 4) was removed through a direct 1½–2-cm. arteriotomy wound. There was a clear plane of cleavage, good back bleeding was established, and the arteriotomy wound was sutured. The pleura was drained through the tenth intercostal space and the thoracotomy and periscapular incisions were closed.

Convalescence was uneventful. The left hand was very warm next day, and the pain in the fingers had disappeared. The thrill over the subclavian artery had disappeared and the blood pressure in the two upper limbs was equal (160/100 mm. Hg). After a few days the temperature of the left hand fell to equal that of the right hand. Eight weeks after the operation the patient was free of symptoms, and the tips of the middle and ring fingers could be separated painlessly.

Histological Report.—Profesor C. E. Lumsden reported on the block removed as follows: "The bulk of the sample appears to consist of hyalinized and partly organized old thrombus, with some calcium in places, but no haemosiderosis. While there is no clear demarcation between the thrombus and the fibrovascular tissue present, and neither endothelium nor muscle is seen, this fibrovascular element

shows such a degree of architectural structure that this layer must be preformed intima; it shows clearly marked proliferation of fibrous tissue and cholesterol deposition. There is therefore clear evidence of atherosclerosis underlying the thrombosis."

Discussion

The clinical picture presented by this patient is similar to those considered to be examples of the thoracic outlet syndrome. Flint (1937) published one of the first accounts of an aneurysm of the third part of the right subclavian artery directly caused by a cervical rib. Eden (1939) reported the cases of three patients having aneurysms to the third part of the subclavian artery extending to the clavicle: in two the cause was thought to be direct damage to the artery by the associated cervical rib, and, in the third, pressure of the artery on the first rib; he subscribed to the thrombo-embolic theory of Lewis and Pickering (1934) to explain associated vascular changes in the hand.

These reports and others put the emphasis on direct damage to the subclavian artery by a cervical or abnormal first rib as the cause of vascular disorders in the upper limb, rather than the effects of irritation of sympathetic nerve fibres. It seemed to be established that a cervical rib or abnormal first rib was the direct agent of damage to the subclavian artery, with consequent thrombosis or aneurysm formation, from which emboli were detached to enter distal arteries. But there are difficulties in this explanation. Many patients have cervical ribs and only a few develop subclavian aneurysms. Cervical ribs are usually bilateral, but subclavian aneurysms are not. Subclavian aneurysms are commonly found proximal to the outer border of the first rib. Resection of a cervical or abnormal first rib, with or without upper dorsal ganglionectomy, seldom gives complete cure, and the use of these procedures in one patient having a cervical rib and subclavian aneurysm did not arrest the progress of the aneurysm (Shucksmith, 1958). In one patient being treated for Raynaud's symptoms in one upper limb no lasting beneficial effect was obtained from cervical rib resection; the other three developed Raynaud's disease, and the upper limb first affected subsequently developed thrombosis of the whole subclavian artery (Shucksmith, 1958).

Shenkin (1957), reporting three cases of thrombosis of the subclavian artery in the presence of cervical rib, described thrombosis of this artery in a 65-year-old patient having bilateral cervical ribs which extended from the origin of the vertebral artery distally to include the brachial artery. Shenkin's and Shucksmith's reports could indicate that primary arterial disease of the subclavian artery could be as much a factor as external pressure on the artery in producing the clinical picture previously ascribed to external pressure alone.

The clinical picture presented in this report indicates clearly that primary arterial disease of the subclavian artery can mimic the picture previously thought to be caused by the external pressure by the scalene muscles or clavicle on the subclavian artery when no cervical rib or band was found. While external pressure as a cause of damage to the subclavian artery with subsequent thrombosis or aneurysm formation is not invalidated, the importance of considering primary arterial disease of the subclavian artery in the costo-clavicular syndrome is established. Atherosclerosis was

found to be the cause of blockage of the first part of the subclavian artery, and it is possible, on this basis, to explain the formation of an aneurysm of the third part of the subclavian artery by assuming that atherosclerosis involves the whole artery, that atheromatous deposits narrow the first part, and that the loss of elasticity in the distal part allows post-stenotic dilatation.

This concept of atherosclerosis as the primary part of the change in the subclavian artery gains credit when the course of the artery, as seen in the normal arteriogram or directly through the open chest, is studied (Figs. 2 and 5). The subclavian artery courses

FIG. 5.—Normal subclavian arteriogram.

high into the neck and there arches gracefully towards the arm—a different picture from that seen through the usual exposure at the root of the neck when the artery seems to be dodging between structures which may nip it or lift it up and injure it. Not only is atherosclerosis suggested as a primary cause of lesions in the subclavian artery but it is suggested that coincidental atherosclerosis of arteries in the arm and forearm, together with a similar condition in the subclavian artery, is a possible explanation of wasting of the upper limb and gangrene of finger-tips. Such an explanation would come into line with comparable changes in the lower limb.

Investigation of a patient suffering from arterial disease of the upper limb is not complete without aortography. It must be borne in mind that any atherosclerotic lesion is always more severe than the aortogram may suggest (contrast Figs. 1, 3, and 4).

Summary

The clinical details and successful management by thrombo-endarterectomy of a patient having an atherosclerotic block of the first part of the subclavian artery is described.

It is suggested that atherosclerosis may be the primary cause of change in the subclavian artery previously ascribed to external pressure.

The importance of aortography to demonstrate the branches of the aortic arch in the thoracic outlet syndrome is emphasized.

I am particularly indebted to Dr. C. Groves and Mr. J. C. Coates, of Hull, for referring this patient; to Dr. P. G. Keates and Dr. M. D. Summerling for the aortograms, and to Miss M. Brown for her diagram of the dissected subclavian artery.

REFERENCES

- Caccamise, W. C., and Whitman, J. F. (1952). *Amer. Heart J.*, **44**, 629.
 Eden, K. C. (1939). *Brit. J. Surg.*, **27**, 111.
 Flint, E. R. (1937). *Ibid.*, **24**, 622.
 Frøvig, A. G. (1946). *Acta psychiat. (Kbh.)*, Suppl. 39.
 Lewis, T., and Pickering, G. W. (1934). *Clin. Sci.*, **1**, 345.
 Martorell, F., and Fabrè Tersol, J. (1944). *Med. clin. (Barcelona)*, **2**, 26.
 Seldinger, S. I. (1953). *Acta radiol. (Stockh.)*, **39**, 368.
 Shenkin, H. A. (1957). *J. Amer. med. Ass.*, **165**, 335.
 Shimizu, K., and Sano, K. (1951). *J. Neuropath. clin. Neurol.*, **1**, 37.
 Shucksmith, H. S. (1958). *Brit. med. J.*, **2**, 1228.
 Takayasu, M. (1908). *Acta Soc. ophthal. jap.*, **12**, 554.
 Towers, J. R. H., Keates, P. G., Newcombe, C. P., and Sumerling, M. D. (1958). *Brit. med. J.*, **2**, 1043.
 Wickbom, I. (1957). *Acta radiol. (Stockh.)*, **48**, 321.

SEQUENTIAL METHODS APPLIED TO THE STUDY OF PROCHLORPERAZINE

BY

P. SAINSBURY, B.A., M.D., D.P.M.

*Director of the Medical Research Council's Clinical
Psychiatry Research Group; Honorary Consultant
Psychiatrist, Graylingwell Hospital, Chichester*

AND

C. J. LUCAS, M.B., M.R.C.P., D.P.M.

*Member of the Medical Research Council's Clinical
Psychiatry Research Group; Senior Registrar,
Graylingwell Hospital, Chichester*

The ability of the pharmaceutical chemists to synthesize compounds of potential therapeutic value in psychiatry is not matched by a corresponding ingenuity in the methods for their clinical evaluation. Consequently the psychiatrist is often baffled by an array of drugs of uncertain therapeutic value and is inclined to criticize the chemist rather than himself for this state of affairs. A need has therefore arisen to develop methods of clinical trial which are rapid and which use simple but reliable criteria of therapeutic effect. Once an overall effect has been established more detailed inquiries can follow. These observations apply particularly to the so-called "tranquillizers"—that is to say, drugs which allay states of over-excitement, such as anxiety and its somatic manifestations, without decreasing alertness and awareness.

Purposes and Design of the Trial

We therefore had two complementary purposes in undertaking a clinical trial of a new tranquillizer. The first was to see if the statistical method of sequential analysis (Armitage, 1954) could be successfully used in a psychiatric drug trial of this kind; if so, the advantages of simplicity in design and of economy in time and numbers of patients treated might be considerable. Our second aim was an attempt to find out whether a new

phenothiazine derivative, prochlorperazine ("stemetil"), was as effective in reducing tension and anxiety in psychoneurotic out-patients as some published studies have claimed.

Prochlorperazine is 1-[3-(2-chloro-10-phenothiazinyl)-propyl]-4-methylpiperazine. It is a member of the phenothiazine series of drugs and its effects are similar to those of chlorpromazine. It is prepared for clinical use in two forms, the dimaleate and the dimethane sulphonate. In dosage of less than 40 mg. of the maleate a day side-effects are not troublesome. Jaundice and blood dyscrasias have not so far been reported.

The drug is probably of most use in the management of schizophrenia, but striking claims have been reported for it in the neuroses. Wennersten (1956) quotes unpublished data on 1,429 patients with various neurotic illnesses in whom the response to prochlorperazine was excellent or good in 73%. Vischer (1957) gave the drug to 38 patients with various organic and psychiatric illnesses and claimed that 21 became completely free of psychoneurotic symptoms. Lesse (1957) claims effective relief of 20 out of 37 patients with moderate anxiety, but observed the drug to be less effective with marked anxiety. McAfoos (1957) found all his 37 patients with anxiety reactions helped by prochlorperazine and psychotherapy. Stevenson (1957), in a study of 100 patients of widely different diagnostic categories, claims good relief of anxiety in 83%. Most authors recommend a dose of 15–20 mg. a day and claim that the response is prompt, either within days or one or two weeks. These trials can be criticized on the grounds that they were uncontrolled, the diagnostic categories were ill-defined or ill-assorted, and the criteria of improvement were unclear.

The statistical method, sequential analysis, determined the design of the present trial. A control treatment (placebo) and the new treatment (prochlorperazine) were both given to each suitable patient as he became available. The patient had to decide which of the two treatments he preferred. The sequential plan used had to meet the following requirements. The proportion of response to the placebo was expected to be at least 35% (Beecher, 1956); but if we were able to detect, with a probability of 0.95, a favourable response to prochlorperazine in 70% of patients, this would be considered a sufficient advantage to justify recommending it. The proportion of preferences in favour of prochlorperazine would depend to some extent on the distribution of assessments on the five-point score described below and on the correlation between the two responses from the same subject, but rough calculations suggest that it would be in the region of 0.8. This is the value of θ (the proportion of untied pairs favouring prochlorperazine) which would be obtained if preferences were based purely on favourable responses (rather than the five-point score) and if there were no correlation between the two responses from a subject (cf. Fig. 2 of Armitage, 1954; Snell and Armitage, 1957).

The trial was to be decided on the outcome of this test. As a further exploration of the application of sequential analysis we attempted to use a measurement of anxiety (the clinical symptom which prochlorperazine was most likely to benefit) as the criterion of the effectiveness of the treatments. The appropriate method in such a case is a sequential t-test. The plan chosen to test the null hypothesis that there is no change in the patients' anxiety scores with prochlorperazine at a significance level of 0.05 is described below.