afibrinogenaemia (Soulier *et al.*, 1952; Baumann, 1952). It may well be, therefore, that dextran carries a risk in this field, as it does in obstetrics.

Summary

Plasma should be preferred to dextran as an emergency blood-volume restorer in conditions in which hypofibrinogenaemia is apt to develop. The most important of these is accidental ante-partum haemorrhage, others being retention of a dead foetus *in utero*, and hydatidiform mole.

The transfusion of dextran or similar preparation in any circumstance should be limited to 1 to 2 pints (0.5 to 1 litre).

Hypofibrinogenaemia can be recognized quickly by a simple thrombin coagulation test before there is clinical evidence of its presence.

In cases of coagulation failure due to fibrinogen deficiency, transfusion of double-strength plasma offers a readily available method of treatment.

I am indebted to Professor T. N. A. Jeffcoate for a great deal of patient criticism and advice. I have to thank Colonel B. Blewitt, Dr. G. Alun Roberts, and Mr. G. Williamson for fibrinogen estimations performed in Newsham General Hospital Laboratory. Dr. D. Lehané kindly made available supplies of plasma. The cases were reviewed by permission of the consultant obstetric staff of Birmingham Maternity Hospital; Queen Charlotte's Hospital, London; Liverpool Maternity Hospital; and Mill Road Maternity Hospital, Liverpool.

REFERENCES

- Adant, M. (1954). *C.R. Soc. Biol. (Paris)*, **148**, 391.
Barnett, V. H., and Cussen, C. A. (1954). *British Medical Journal*, **2**, 676.
Barry, A. P., Feeney, J. K., and Geohagan, M. D. (1955). *Ibid.*, **2**, 12.
Baumann, J. (1952). *Rev. Hémat.*, **7**, 20.
Carbone, J. V., Furber, F. W., Scott, R., and Crosby, W. H. (1954). *Proc. Soc. exp. Biol. (N.Y.)*, **85**, 101.
De Lee, J. B. (1901). *Amer. J. Obstet.*, **44**, 785.
Fletcher, F., Martin, L. E., and Ratcliffe, A. H. (1952). *Nature (Lond.)*, **170**, 319.
Hodgkinson, C. P., Luzadre, J. H., Piper, P. W., Swinehart, L. A., and Remp, D. G. (1955). *Obstet. and Gynec.*, **5**, 465.
Laurell, A. B. (1951). *Scand. J. clin. Lab. Invest.*, **3**, 262.
Lehané, D., Kwantes, C. M. S., Upward, M. G., and Thomson, D. R. (1949). *British Medical Journal*, **2**, 572.
Lepage, F., Eyquem, A., and Petit, P. F. (1952). *Rev. Hémat.*, **7**, 72.
McKay, D. G., Merrill, S. J., Weiner, A. E., Hertig, A. T., and Reid, D. E. (1953). *Amer. J. Obstet. Gynec.*, **66**, 507.
— Littlejohn, T. W., and Schoenbucker, A. K. (1955). *Obstet. and Gynec.*, **5**, 85.
Reid, D. E., Weiner, A. E., and Roby, C. C. (1953). *Amer. J. Obstet. Gynec.*, **66**, 465.
Ricketts, C. R. (1952). *Nature (Lond.)*, **169**, 970.
Schneider, C. L. (1951). *Surg. Gynec. Obstet.*, **92**, 27.
— (1952a). *Amer. J. Obstet. Gynec.*, **63**, 1078.
— (1952b). *Ibid.*, **64**, 141.
Soulier, J. P., Mathey, J., Le Bollock, A. G., Daumet, P., and Fayet, H. (1952). *Rev. Hémat.*, **7**, 30.
Weiner, A. E., Reid, D. E., and Roby, C. C. (1950). *Amer. J. Obstet. Gynec.*, **60**, 379.

In 1951 the London County Council decided to improve the main drainage works at Northern Outfall, which were constructed in 1864 as part of the Metropolitan Board of Works scheme for the collection and disposal of sewage. The new construction is to ensure the adequate treatment of sewage, and is the council's contribution to the improvement of the quality of Thames water, which has deteriorated recently. Work at present in hand, or proposed, includes the finishing of the detritus pits started before the war; the construction of primary sedimentation channels to treat up to 200 million gallons (909 million litres) per day; sludge digestion plants to treat up to 4,000 tons (4 million kg.) of sludge per day; and a diffused air plant to treat an additional 60 million gallons (273 million litres) of sewage effluent per day. The total cost is estimated to be about £8,465,000. The whole of the sludge produced will be digested, and 2½ million cubic feet (70,000 cubic metres) of methane gas will be available as power for driving the eight 960-horse-power gas turbines to be installed in the power house. By the end of 1957 these works should be operating and the condition of the effluent discharged into the river made satisfactory at all times.

USE OF CORTICOTROPHIN GEL AND CORTISONE IN TREATMENT OF SEVERE AND INTRACTABLE ASTHMA

BY

BRIAN M. DAVIES, M.B., M.R.C.P., D.C.H.

Medical Registrar, United Cardiff Hospitals

AND

D. A. WILLIAMS, M.D., M.Sc., F.R.C.P.

Physician, United Cardiff Hospitals

In the same year as Hench *et al.* (1949) reported the dramatic effect that cortisone produced in rheumatoid arthritis, Bordley *et al.* (1949) reported the "unequivocal benefit within 4-48 hours" that five chronic asthmatics derived from injections of corticotrophin. Since 1949 there have been many reports from abroad (including Carey *et al.*, 1950; Rose *et al.*, 1951; Schwartz, 1951; Shulman *et al.*, 1951; Baldwin and de Gara, 1952; Arbesman *et al.*, 1952; Baldwin *et al.*, 1955), and a few from this country (Ball, 1954; Savidge and Brockbank, 1954; Pearson, 1955), confirming the striking, though temporary, relief that can be obtained in the large majority of cases of otherwise intractable asthma with short courses of corticotrophin or cortisone.

Gay and Murgatroyd (1954) reported favourably on their results with corticotrophin gel in 76 patients. They gave only one injection a day, and emphasized the value of this therapy in "ambulatory" patients, thus avoiding the cost of hospital admission.

Long-term continuous therapy with these hormones is also being reported, and indications are that continued relief can be obtained (Baldwin *et al.*, 1955).

There are contraindications to the use of these hormones, and some cases of asthma do not respond. Furthermore, the relief produced is only temporary, symptoms recurring soon after the treatment is stopped. It is the main purpose of this article to measure the results of short-term therapy with cortisone, corticotrophin, and hydrocortisone in cases of severe and/or intractable asthma.

Material and Methods

Our observations are based on 63 courses of treatment on 50 adult patients—44 asthmatics (Table I) and 6 chronic bronchitics with persistent wheezing. The six chronic bronchitics were all male, their ages ranging from 37 to 66 years.

TABLE I.—Data on the 44 Asthmatics

	Sex		Present Age		Type of Asthma	
	Male	Female	Under 40 Years	40+ Years	Extrinsic	Intrinsic
No. of cases	12 (27.3%)	32 (72.7%)	9 (20.5%)	35 (79.5%)	2 (4.5%)	42 (95.5%)

The youngest was aged 17, two were over 70.

Twenty of the patients were treated by Dr. Leslie Gay, of the Johns Hopkins Hospital, when he visited Cardiff in June, 1954, bringing with him supplies of corticotrophin gel and hydrocortisone. As requested by Dr. Gay, they were patients whose asthma had been intractable to all previous therapy: 10 were treated as out-patients and 10 as in-patients. The remaining 30 were treated in hospital, and whether corticotrophin or cortisone was used depended mainly on its availability.

Before treatment was started a careful history of the patient was taken and physical examination made: all had radiographs of the chest and sinuses, all asthmatics were skin-tested, most had electrocardiograms taken, and daily vital capacity estimations and eosinophil counts were made.

Before it was decided whether or not to use cortisone or corticotrophin, each patient was specifically asked if he or she had had a peptic ulcer or if there had been any dyspepsia at all. Peptic ulceration is a definite contraindication to the use of these hormones, and a few cases were excluded because of recent duodenal ulceration. One patient who had had a proved duodenal ulceration sixteen years previously but no symptoms since was included. Inquiry and examination were also made regarding a "nervous breakdown," diabetes, tuberculosis, and hypertension, but no patient was excluded on these grounds.

Eleven of the asthmatics were having very severe attacks, and were treated within twenty-four hours of admission to hospital, having failed to respond to subcutaneous adrenaline and intravenous aminophylline. The other 33 were of the chronic intractable type, and had failed to respond to a reasonable period of antispasmodics, antibiotics, sedation, and breathing exercises.

Corticotrophin gel was used alone in 27 courses of treatment, in one case a course of corticotrophin only was given, and in 17 courses cortisone was used alone. Corticotrophin gel was given and followed by hydrocortisone tablets in 15 courses and corticotrophin gel was followed by cortisone in three.

The corticotrophin gel was given deeply intramuscularly with a *dry syringe* and a 20-gauge needle. The gel was liquefied by standing in warm water or by being held in the hand, and no difficulty was experienced in giving it, nor did the patients complain of any untoward pain. Dr. Gay used 60 to 100 units on the first day, depending on the severity of the symptoms; 60 to 80 units on the second and third days; 20 to 60 units on the fourth and subsequent two or three days, depending entirely on the individual response; followed by hydrocortisone for six to twenty days. In general, on the chronic intractable in-patients we used 80 units daily for four days, followed by 40 units for three days.

The dose of cortisone used in status asthmaticus was 300 mg. in divided doses on the first day, 200 mg. on the second day, and 100 mg. on the third day. This dose was repeated on subsequent days or reduced according to the patient's progress. In chronic intractable asthma the usual dose was 100 mg. a day for four days, followed by 75 mg. a day for three days. If the initial dose of 100 mg. was not effective 300 mg. was usually given for a few days. As symptoms subsided so dosage was lowered until the chest had been clear for a few days. In the main, treatment was continued for seven to fourteen days.

In addition to these hormones, a mixture containing 2 g. of potassium acetate in each $\frac{1}{4}$ oz. (14 g.) was given three times a day and a diet low in sodium with added vitamin C. When hormone treatment was started in-patients continued with physiotherapy and some with antibiotics. All were allowed to use antispasmodic measures, inhalers, or tablets as required, and their use was noted.

The diagnosis of asthma was made mainly on the history of recurrent attacks of spontaneous dyspnoea and wheeziness. Chronic bronchitis was diagnosed in those patients who had persistent wheeziness but no spontaneous paroxysms of dyspnoea. This differentiation is sometimes difficult, but in view of the essential differences in their pathology (Gough, 1955) and their apparent differences in response to hormonal therapy it is clearly important. The classification into intrinsic and extrinsic asthma (Rackemann, 1940) was made because of its general acceptance and because of the difficulties in assessing the relative importance of the infective and psychological factors which are the dominant factors in the majority of chronic asthmatics. Assessment of pro-

gress was made daily. Our results were recorded as good, fair, and poor. "Good" meant complete subjective relief with complete, or nearly complete, clearing of the chest of adventitious sounds; "fair" and "poor" meant some and no improvement respectively. When the patients left hospital they were seen weekly at the asthma clinics.

Results in Asthmatics

The results of 56 courses of treatment in 44 asthmatics are shown in Table II.

TABLE II.—Table of Results in Asthma

	Good	Fair	Poor	Deaths	Total
No. of courses ..	49 (87.5%)	3 (5.3%)	3 (5.3%)	1 (1.8%)	56

Death.—One patient died in this series—a woman of 53 who was admitted with severe intractable asthma and was treated with antibiotics and antispasmodics for thirty days. Her condition deteriorated, and she was then given daily 300 mg., 200 mg., 100 mg., and 100 mg. of cortisone, when she died. At necropsy the typical findings in death from asthma—widespread plugging of the bronchi—were present. It is clear that death was due to failure to relieve her asthma, and not to the cortisone itself.

Poor Results.—The three poor results occurred in two women and one man. The man, aged 54, failed to respond after 625 mg. of cortisone over seven days with a maximum daily dose of 100 mg. Six days later he was given corticotrophin gel with a good response. One woman, aged 71, failed to respond after 450 units of corticotrophin gel with a maximum daily dose of 75 units. A week later her chest cleared after a course of oxytetracycline ("terramycin"). The second woman, aged 38, failed to respond to 475 units of corticotrophin gel over five days with a maximum daily dose of 75 units, followed by 1,200 mg. of cortisone over eight days, with a maximum daily dose of 300 mg., although she had a marked fall of eosinophils. Treatment was stopped on account of calf-vein thrombosis and pulmonary embolism. She was continued on antibiotics, and in four weeks her chest cleared. All three cases had a heavy purulent sputum.

Fair Results.—Only fair results were obtained in three courses. One of these was due to the use of 10 units of corticotrophin gel daily for five days, a dose which was obviously too small. The other two fair results both occurred in a woman of 62 years who had had many months of intractable asthma. On the first admission, after having 450 units of corticotrophin gel with a maximum daily dose of 75 units over seven days (after a previous week of antibiotic treatment), there was only slight improvement. On her second admission, in status asthmaticus, she responded well to cortisone. On her third admission, a month later, she again had only a fair response to corticotrophin gel, 600 units given over eight days with a maximum dose of 75 units. At this time a right middle-lobe collapse was present, and the sputum was heavily purulent.

Good Results.—Good results were obtained in the two extrinsic asthmatics and in the remaining intrinsic cases. The improvement in the out-patients under Dr. Gay's treatment was very striking: one of his patients had to be wheeled into the clinic on account of a severe exacerbation of her asthma, and her response without hospital admission was an excellent example of what Dr. Gay has emphasized. With the in-patients, the reduction of their period of disability compared with that previously experienced with chronic asthmatics was also most striking. We no longer have our beds held up for weeks or months with several cases of intractable asthma. This is apart from the relief experienced by the patients. The assessment of the cases of status asthmaticus in this group is more difficult, but all cases had failed to respond to adrenaline and adequate doses of intravenous aminophylline, and hormonal treatment appeared to us to be life-saving in many cases.

Results in Chronic Wheezy Bronchitis

Our cases of wheezy bronchitis are too few for any conclusions to be drawn on the effect of hormonal therapy in chronic bronchitis, but it would appear that there was an essential difference between the response of asthmatics as a group and the chronic bronchitics. Our bronchitis cases were given similar treatment to the asthmatics, yet in only two were the results good (Table III). In neither of these was the relief as dramatic as was usual with the asthmatics.

TABLE III.—Results in Chronic Bronchitis

Males	Average Age	Courses of Treatment	Results		
			Good	Fair	Poor
6	56	7	2	3	3

TABLE IV.—Complications of Treatment (Excluding the One Death)

No. of courses	None	Slight	Severe	Doubtful	Total
..	46 (74.2%)	10 (15.9%)	3 (4.8%)	1	60

Complications (Table IV)

A moderately severe melaena occurred in a man of 66 years with a proved duodenal ulcer sixteen years ago when he had had a barium meal examination, but who had had no gastric symptoms since. Two patients had severe and painful furunculosis.

The case classed as doubtful was that of a woman of 38. She developed a pulmonary infarction and calf-vein thrombosis (previously mentioned) after six weeks in bed, and so cortisone cannot definitely be incriminated, despite its known influence on blood-clotting mechanisms (Chatterjea and Salomon, 1954).

Five patients developed varying degrees of oedema, but in none was it severe, and all cleared rapidly, mercurial diuretics being used in three. A slight hypertension occurred in two patients, one of them having a transient glycosuria, while another patient also developed a transient glycosuria. "Moonface" and slight euphoria occurred in two patients.

There is general agreement that, when these hormones are given in properly selected cases for short periods, side-effects are infrequent and relatively mild. Constant care, however, is necessary.

Periods of Remission

The periods of remission varied from one day to 240 days, with an average of 30.3 days.

The results following 42 courses are given in Table V. It will be seen that 43% had over three weeks' complete remission of symptoms. The natural remissions which occurred

TABLE V.—Duration of Remission of Asthma after 42 Courses

Length of Remission	No.	%
Less than 3 days	3	7
3-10 days	13	31
11-20 days	8	19
21 days to 5 weeks	10	24
5 weeks to 8 weeks	2	5
Over 2 months	6	14
		43

Average period of remission, 30.3 days. Maximum period of remission, 240 days.

in our two seasonal asthmatics have not been included: the remissions during the season, which occurred on terminating therapy, were of two days and seven days. The more severe of the two was then given further hormone therapy to the end of the season, with good results.

A later follow-up between three and ten months after the 41 asthmatics had had their last course gave these findings: 6 (15%) have had very little asthma since; 16 (39%)

have had varying degrees of moderately severe asthma, necessitating supervision at the clinic; 8 (20%) have had moderately severe, in some cases severe, asthma hardly controlled by the clinic therapy (if supplies of the hormones had been more easily obtainable they would have had continuous therapy); 11 (26%) were receiving maintenance therapy.

Thus, of these cases of severe asthma, 19 (46%) would ideally require the use of more continuous therapy. These are, of course, only a very small proportion of those attending the asthma clinics: our figures suggest such a requirement in 1 in 80 to 1 in 100 of adult clinic patients.

Dosage of Corticotrophin Gel and Cortisone

Bayliss and Steinbeck (1954), in estimating the plasma steroid level after corticotrophin gel injections, noted that the response varied in different patients and that 20 or 80 units might in different patients raise the plasma steroids to the same level. They found no constant elevation of the plasma steroids twenty-four hours after corticotrophin gel, but, with Gay and Murgatroyd (1954), we have found one injection a day to be sufficient in chronic intractable asthma.

As already indicated, we have found the dose required varies with the severity of the asthma, 100 to 60 units of corticotrophin gel on the first day, 80 to 60 units on the second day, etc., and that for the average intractable asthmatic in hospital, a suitable basis for dosage is 80 units daily for four days, followed by 40 units for three days.

Baldwin *et al.* (1955), in very severe asthma, used 40 units every four hours for twenty-four hours (240 units), reducing the dose with improvement to six-hourly, then eight-hourly, and within the week the patients were well on 40 units twice daily; the dosage was then reduced to once a day. They found 40 units daily usually sufficient for the ambulatory intractable asthmatic. With cortisone, also, they recommend larger doses than we have used for severely ill asthmatics—that is, 100 mg. every four hours for the first twenty-four hours (600 mg.)—and state that within a week patients are doing well on 25 mg. three or four times a day. For the intractable case their initial dose of 100 mg. a day is the same as ours. Our dose of 25 mg. four times a day for four days, followed by 25 mg. three times a day for three days, was effective in the average intractable case, although a few needed 300 mg. a day for a few days.

Dosage schemes, however, are not to be laid down by rule of thumb, but should depend on the severity of the asthma and on the patient's response. Symptomatic relief and eosinopenia do not go hand in hand, and present laboratory tests are of little value in guiding dosage.

In the recent literature it is generally agreed that whether the asthma is dominantly allergic, psychological, or infective does not affect its response. Both our extrinsic (allergic) cases responded well, as did the large majority of our intrinsic cases. It was our finding, in common with other workers, that a patient found intractable during one course might respond to a later course. In some of our cases this could have been accounted for by differences in dosage, but not invariably so.

Bickerman and Barach (1954) found that corticotrophin was generally more effective than cortisone and that hydrocortisone was superior to both. Our experiences are too limited to warrant a definite statement, but we have the impression that, in the dosage we used, corticotrophin gel was generally more effective than cortisone. However, deaths have been recorded after corticotrophin (Hill and Swinburn, 1954; Bloom and Wolff, 1954), while the convenience of being able to give cortisone by mouth is an advantage.

Immediate Response and Failure to Respond

Gay and Murgatroyd (1954) reported excellent or good results with corticotrophin gel in 82% of 76 severe asthmatics, moderate or fair results in another 5%, and poor

results or failure in 13%. Baldwin *et al.* (1955) reported satisfactory results in 87% of 60 asthmatic patients using corticotrophin gel and/or cortisone. Kania and Schmidt (1954) found that 76.6% of 111 patients were completely relieved. Our good results (87.5%) are very similar. The general agreement that the large majority of chronic intractable asthmatics can be relieved even temporarily is obviously important, as is the relative absence of dangerous complications if care is taken to exclude cases with peptic ulceration and the other conditions mentioned previously.

The general agreement that a small but definite proportion fail to respond to hormonal therapy is a challenge, and is intriguing. The exact mode of action of these hormones is not known, nor are we sure of exactly what is happening in the bronchi when a patient is wheezing. In those patients who die from status asthmaticus and in whom post-mortem examination shows mucous plugging of the bronchi, the inadequacy of the dose or its late administration would appear to be the cause of failure. Analogy with the use of insulin in diabetic coma is perhaps appropriate.

The importance of distinguishing between asthma and bronchitis has already been pointed out, but it may also become important to distinguish between an attack of bronchitis and an attack of asthma in an asthmatic. We were impressed by the failure of response in one of our patients who had a purely purulent sputum, even though there was a marked eosinophilic drop in the blood, and by the fact that her condition later improved on antibiotics and general measures. Possibly the hormones given relieve asthma due to non-purulent obstruction of the bronchi, but fail to relieve the obstruction due to a frankly purulent bronchitis.

Duration of Response and Need for Maintenance Therapy and Dangers of Treatment

It is of interest that in some of our cases there was a long period of comparative freedom after hormone therapy. This may well have been due to the antibiotic therapy and general measures which they had in hospital, or to a natural remission as mentioned by Savidge and Brockbank (1954). Most of our cases were of the infective type, and many had antibiotics before, during, and after hormonal therapy. All writers are agreed that search into the underlying cause of the asthma and its treatment is still essential.

Of equal interest have been the subsequent requirements of our patients. Our estimate that some 40–50% of them might ideally need maintenance therapy is very closely paralleled by the findings of Baldwin *et al.* (1955). Thirty of their original 60 patients required maintenance therapy. Eleven of our patients have had continuous therapy. Complications known to occur on prolonged treatment include decalcification of the skeleton, Cushing's syndrome, increasing weight, secondary infection, and psychosis. Stoner and Whiteley (1954) have shown at necropsy that continuous cortisone therapy results in an atrophic inactive adrenal gland, while corticotrophin therapy leads to an enlarged active gland. Under adverse conditions disuse atrophy might indeed impair the asthmatic's response to "stress"; yet, so far, clinical reports indicate that this atrophy is reversible (Englemann *et al.*, 1953; Irwin *et al.*, 1954). Savidge and Brockbank (1954) have drawn attention to deaths from asthma that occurred while patients were on continuous cortisone therapy; they believe that the suppression of spontaneous adrenal activity by cortisone therapy might have been partly responsible for these deaths. This possibility must, of course, be considered. We must not, however, forget that deaths from status asthmaticus occur in approximately 3,000 patients each year in England and Wales (Williams, 1953).

Continuous hormonal therapy is beset with known and even possibly unknown risks and needs very careful supervision. We find the smallest dose of cortisone (generally 12.5 to 75 mg. a day) that will keep the patient moderately comfortable with the help also of antispasmodics and not

necessarily free from all symptoms. In addition we give corticotrophin gel, 20 units twice a week (Gottlieb, 1954). Any superadded chest infection is immediately treated with antibiotics.

So far we have no cause to regret our use of maintenance therapy, while its effect on our patients has often been most satisfactory.

It is encouraging to read the observations of Baldwin *et al.* (1955) that "in general it may be stated that the longer the hormone therapy is continued the smaller the amount of the drug that is required, if the factors leading to the asthma are progressively treated and managed."

Caution is still, however, very necessary in continuous therapy, but short courses appear to be quite safe if care is taken in the selection of cases.

Summary and Conclusions

The effects of treating 44 chronic asthmatics and 6 chronic bronchitics with 57 and 7 courses respectively of cortisone, corticotrophin gel, and/or hydrocortisone are reported.

Eleven of the asthmatics were in status asthmaticus, the remaining 33 had intractable asthma. In the asthmatics 87.5% of the courses gave good results. The temporary relief afforded lasted on an average thirty days. Continuation of hormonal therapy in these severe and intractable asthmatics was unnecessary in 50% or more, but appeared desirable in some 40 to 50%. Contraindications, complications, and dosage schemes are discussed.

The importance of distinguishing between asthma and bronchitis is emphasized.

It is with pleasure that we acknowledge our considerable indebtedness to Dr. Leslie Gay, of the Johns Hopkins Hospital, Baltimore, U.S.A.; to Armour Laboratories for supplies of corticotrophin gel, and to Merck and Co. for supplies of "hydrocortone"; and to Professor H. Scarborough and Dr. E. H. Evans, of Church Village, for supplies of cortisone and corticotrophin gel.

REFERENCES

- Arbesman, C. E., Schneider, M. A., Greene, D. G., and Osgood, H. (1952). *J. Allergy*, **23**, 293.
- Baldwin, H. S., and de Gara, P. F. (1952). *Ibid.*, **23**, 15.
- Spielman, A. D., and Dworetzky, M. (1955). *Ibid.*, **26**, 44.
- Ball, K. (1954). *Lancet*, **1**, 1162.
- Bayliss, R. I. S., and Steinbeck, A. W. (1954). *British Medical Journal*, **1**, 486.
- Bickerman, H. A., and Barach, A. L. (1954). *J. Allergy*, **25**, 312.
- Bloom, A., and Wolff, F. (1954). *British Medical Journal*, **2**, 1354.
- Bordley, J. E., Carey, R. A., Harvey, A. McG., Howard, J. E., Kattus, A. A., Newman, E. V., and Winkenwerder, W. L. (1949). *Bull. Johns Hopk. Hosp.*, **85**, 396.
- Carey, R. A., Harvey, A. McG., Howard, J. E., and Winkenwerder, W. L. (1950). *Ibid.*, **87**, 387.
- Chatterjee, J. B., and Salomon, L. (1954). *British Medical Journal*, **2**, 790.
- Englemann, E. P., Krupp, M. A., Johnson, H. P., Welsh, J. E., Wrenn, H. T., and King, W. R. (1953). *Arch. intern. Med.*, **91**, 1.
- Gay, L. N., and Murgatroyd, G. W. (1954). *J. Mich. med. Soc.*, **53**, 33.
- Gottlieb, P. M. (1954). *Ann. Allergy*, **12**, 456.
- Gough, J. (1955). *Lancet*, **1**, 161.
- Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1949). *Proc. Mayo Clin.*, **24**, 181.
- Hill, B. H. R., and Swinburn, P. D. (1954). *Lancet*, **1**, 1218.
- Irwin, J. W., Henneman, P. H., Wang, D. W. K., and Burrage, W. S. (1954). *J. Allergy*, **25**, 201.
- Kania, E., and Schmidt, P. (1954). *Munch. med. Wschr.*, **96**, 759.
- Pearson, J. E. G. (1955). *British Medical Journal*, **1**, 189.
- Rackemann, F. M. (1940). *J. Allergy*, **11**, 147.
- Rose, B., Pare, J. A. P., Pump, K. K., and Stanford, R. L. (1951). *Proc. 2nd clin. A.C.T.H. Conf.*, **2**, 414.
- Savidge, R. S., and Brockbank, W. (1954). *Lancet*, **2**, 889.
- Schwartz, E. (1951). *J. Amer. med. Ass.*, **147**, 1734.
- Shulman, L. E., Harvey, A. McG., Howard, J. E., and Schoenrich, E. H. (1951). *Proc. 2nd clin. A.C.T.H. Conf.*, **2**, 401.
- Stoner, H. B., and Whiteley, H. J. (1954). *Lancet*, **2**, 992.
- Williams, D. A. (1953). *Thorax*, **8**, 137.