1957) as compared with that in healthy subjects, the drug may be said to correct this abnormality.

These results are probably relevant to the response to ordinary food, since the test meal used in this work is thought to stimulate gastric secretion by virtue of its volume (Macdonald and Spurrell, 1953; Hunt and Macdonald, 1954), a property necessarily common to all meals. Further work is required to decide whether nacton inhibits secretion in response to other modes of stimulation.

In view of the numbers of drugs which have been tried it is not surprising that another drug with atropine-like action has been found which will depress the gastric secretion of acid, but as compared with atropine the degree of specificity and the duration of its action are interesting. In our experience the maximal inhibition of gastric secretion was often obtained with doses of nacton which produced no noticeable side-effects. The finding that the fall in the gastric secretory response to test meals persisted for up to three days after the drug was discontinued seems worth further study.

Clinical Use of Nacton.—The study reported here was made under conditions remote from those under which inhibitors of gastric secretion can ordinarily be used, and it is clearly undesirable that the dose of nacton should have to be regulated by measurements of the gastric secretory response. However, our finding that full inhibition of gastric secretion of acid was often achieved by doses which produced no side-effects provides a means of regulating the dose by increasing it at four-day intervals from 2 mg. six-hourly to 3, 4, and 5 mg. six-hourly, and so on until side-effects are observed. The reduction of the dosage by one step abolished side-effects and usually gave satisfactory control of the secretion of acid. We observed in two patients that a dose of the drug adjusted to no side-effects on continuous use gave side-effects if it was restarted after seven days' omission. Where a short period of tachycardia, of urinary retention, of constipation, or of pupillary dilatation must be avoided the drug is contraindicated.

Summary

Twenty-three patients with duodenal ulcer and two with gastric ulcer were given six-hourly doses of nacton ((1-methyl-2-pyrrolidyl) methyl benzilate methyl methosulphate; I.S. 499), a drug with an atropine-like action of long duration, while they were in hospital. For each patient the final dose chosen was that which produced no side-effects. The changes in gastric secretion of acid were studied with test meals. Fourteen of these patients were treated as out-patients and studied with further test meals.

In the second 10 patients the gastric secretion of acid was reduced by half during a period between two hours and eight to nine hours after taking the drug.

Effective dosages of nacton produced little change in the rate of gastric emptying and no change in the mean output of gastric non-parietal secretions.

We are grateful to Drs. C. G. Baker, E. R. Boland, R. T. Grant, A. C. Hampson, R. Kauntze, W. N. Mann, and K. S. MacLean and their colleagues for their unfailing co-operation in this study of patients under their care. Messrs. C. L. Bencard Ltd. kindly gave us large amounts of nacton.

REFERENCES

Acred, P., Atkins, E. M., Bainbridge, J. G., Brown, D. M., Quinton, R. M., and Turner, D. H. (1957). *Brit. J. Pharmacol.*, **12**, 447.
Douthwaite, A. H., Hunt, J. N., and Macdonald, I. (1957). *Brit. med. J.*, **2**, 275.
Doyle, F. P., Mehta, M. D., Sach, G. S., and Pearson, J. (1958). *J. chem. Soc.* In press.
Fisher, R. B., and Hunt, J. N. (1950). *J. Physiol.*, **111**, 138.
Hunt, J. N. (1954). *Guy's Hosp. Rep.*, **103**, 161.
—— (1957). *Brit. med. J.*, **1**, 681.
—— and Macdonald, I. (1954). *J. Physiol.*, **126**, 459.
Kirsner, J. B., and Palmer, W. L. (1953). *J. Amer. med. Ass.*, **151**, 798.
Macdonald, I., and Spurrell, W. R. (1953). *J. Physiol.*, **119**, 259.
Rafsky, H. A., Fein, H. D., Breslaw, L., and Rafsky, J. C. (1954). *Gastroenterology*, **27**, 21.

ALOPECIA FOLLOWING TREATMENT WITH DEXTRAN SULPHATE AND OTHER ANTICOAGULANT DRUGS

BY

G. R. TUDHOPE, B.Sc., M.B., M.R.C.P., M.R.C.P.Ed.
Lecturer in Therapeutics

H. COHEN, M.B., M.R.C.P.
Senior Medical Registrar

AND

R. W. MEIKLE, M.B., M.R.C.P.
Senior Medical Registrar

Department of Pharmacology and Therapeutics, University of Sheffield, and United Sheffield Hospitals

Dextran sulphate has a pharmacological action similar to that of heparin (Ricketts, 1952; Walton, 1952). It differs from heparin in its more prolonged anticoagulant and greater cumulative effects (Ricketts *et al.*, 1953; Donzelot *et al.*, 1955; Jeavons *et al.*, 1956; Cohen and Tudhope, 1956). The commonest toxic effect of dextran sulphate is transient alopecia, which has been described in about 10% of cases (Donzelot *et al.*, 1955; Jeavons *et al.*, 1956), but the frequency of this complication has probably been underestimated, because it may not appear until several weeks after treatment has been stopped. Hjort and Stormorken (1957) have described 10 cases treated with high dosage of dextran sulphate in which loss of hair developed 8 to 10 weeks later. We previously reported that 3 out of 11 patients treated with dextran sulphate developed loss of hair (Cohen and Tudhope, 1956); when these patients were followed up for a longer period the incidence of alopecia was found to be much greater, and we now report the occurrence of this and other toxic effects in 27 patients treated with dextran sulphate. The incidence of alopecia was also studied in 60 patients treated with heparin and an anticoagulant of coumarin type.

Clinical Data

Three groups of patients were studied: those in the first group received dextran sulphate alone; in the second group dextran sulphate was given with a coumarin drug; and in the third group heparin and a coumarin drug were used.

Group 1: Dextran sulphate (total dose 90,000 or more units).—Dextran sulphate was given by repeated intravenous injection to 15 patients. The individual dose was kept constant at 5,000 units, and the frequency of injection was varied in order to maintain the clotting-time at more than twice the value before treatment. It was found that, whereas injections were required eight-hourly during the first 24 hours, 12-hourly dosage was sufficient after 24 to 48 hours, and after 5 to 11 days of continuous treatment one injection every 24 hours was sufficient (Cohen and Tudhope, 1956).

Group 2: Dextran sulphate (total dose less than 40,000 units) with an oral anticoagulant.—Dextran sulphate was given concurrently with ethylbiscoumacetate or phenindione to 12 patients, 5,000 units being injected intravenously eight-hourly for 24 to 48 hours. Treatment was then continued with the oral anticoagulant, the dose of which was regulated to maintain the one-stage prothrombin time two to two and a half times the normal control. The average daily dose of ethylbiscoumacetate was 442 mg.; of phenindione it was 100 mg.

Group 3: Heparin and oral anticoagulant.—Heparin was given with an oral anticoagulant to 60 patients, in whom acute myocardial infarction was diagnosed in 46, pulmonary embolism in 12, and thrombosis of the leg veins in two. In

35 cases heparin was given by intravenous injections of 5,000–15,000 units at intervals of six to eight hours. The total amount of heparin injected is shown in Fig. 1. Administration of ethylbiscoumacetate (18 cases) or phenindione (17 cases) was started concurrently with the heparin, and was continued for 21 to 28 days in most cases. In 25 cases two intramuscular injections of 20,000 units of heparin were given at an interval of 12 hours; phenindione was started simultaneously and was continued for 21 to 28 days. The average daily dose of ethylbiscoumacetate in this group of cases was 660 mg.; of phenindione it was 110 mg.

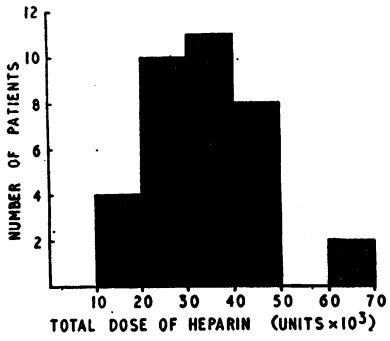

FIG. 1.—Total dose of heparin given by intravenous injection to 35 patients treated with heparin and an oral anticoagulant.

Patients in all groups were examined at least once, three to 12 months after the course of anticoagulant treatment, and most were seen on several occasions during that period. Each patient was specifically questioned about changes in the hair. In a few cases treated with dextran sulphate, alopecia occurred as long as two months after stopping treatment; therefore only patients who could be followed up for at least three months after treatment were included in this study.

Results

The occurrence of alopecia and other toxic effects in patients treated with dextran sulphate is shown in Tables I and II.

Dextran Sulphate—Total Dose at Least 90,000 Units

Alopecia.—Fifteen patients received 90,000 or more units of dextran sulphate, and eight of these developed severe alopecia, amounting to an almost complete loss of scalp hair in six; in addition, loss of pubic, axillary, and facial hair occurred in three patients. Three of those who suffered severe loss of scalp hair were women, one of whom had complete loss of axillary and pubic hair and partial loss of eyebrows. Two male patients reported that they had to shave much less often than normally for a few weeks. The loss of hair was diffuse, affecting the whole scalp, and was unassociated with any apparent change in the scalp itself; it was first noticed three to eight weeks after stopping treatment. Regrowth of hair was obvious after a further four to twelve weeks, and in all cases the hair eventually returned to normal. In one other patient a small occipital bald patch was noticed for the first time 10 days after starting treatment with dextran sulphate. This area of baldness remain unchanged during the following year. In this patient the type of alopecia was different, and it appeared much earlier in the course of treatment than in the other cases, so it is doubtful whether it was related to the dextran sulphate therapy.

Changes in Nails.—In three patients who developed severe alopecia, marked changes in the finger-nails occurred two to three months after dextran sulphate therapy, the nails becoming brittle and transversely ridged. In two of these patients all finger-nails split transversely, the distal parts of the nails being shed. In a fourth patient who did not develop any alopecia, transverse ridging of all finger-nails was noticed six weeks after stopping treatment. In all cases the nails eventually regrew normally.

Diarrhoea.—Severe diarrhoea with the passage of blood in the stools occurred in two patients after treatment with dextran sulphate for 14 days. The total doses were 140,000 and 185,000 units; in fact, these two patients received a larger average daily dose than any other patients in this series. Sigmoidoscopic examination showed that the mucosa was diffusely congested, but neither ulceration nor other local lesion was seen. The diarrhoea persisted for seven days after stopping dextran sulphate. Two other patients had mild diarrhoea, without blood in the stools, after receiving total doses of 90,000 and 130,000 units of dextran sulphate. There was no apparent correlation between the occurrence of diarrhoea and of alopecia. Of the eight patients with severe loss of hair, only two had diarrhoea, which was mild in both cases.

Reduction in Platelets.—Repeated platelet counts were carried out in four patients during treatment with dextran sulphate. A substantial fall in the platelet count occurred

TABLE I.—*Incidence of Alopecia and Other Toxic Effects after Treatment with Dextran Sulphate (Total Dose 90,000 Units or More). Recent Myocardial Infarction was Diagnosed in All Patients Except Nos. 7 and 14, who had Severe and Persistent Angina Following a Previous Myocardial Infarction*

Case No.	Sex	Age (Yrs.)	Duration of Treatment (Days)	Total Dose of Dextran Sulphate (Units)	Loss of Hair	Changes in Nails	Other Toxic Effects
1	M	53	25	205,000	+	+	—
2	M	45	30	195,000	+	—	—
3	M	63	14	185,000	—	—	Diarrhoea; blood in stools
4	M	53	21	185,000	+	+	—
5	M	58	23	180,000	—	—	—
6	M	65	22	160,000	—	+	—
7	M	60	24	160,000	+	+	—
8	M	52	14	140,000	(+)	—	Diarrhoea; blood in stools; sore tongue; anorexia
9	M	56	18	140,000	—	—	—
10	F	62	22	135,000	+	—	Anorexia
11	F	66	19	130,000	—	—	—
12	F	63	20	130,000	+	—	Diarrhoea
13	M	57	14	125,000	—	—	—
14	M	45	19	125,000	+	—	—
15	F	71	11	90,000	+	—	Diarrhoea

In Case 8 the loss of hair was slight (see text).

TABLE II.—*Incidence of Alopecia after Treatment with Dextran Sulphate and an Oral Anticoagulant Drug*

Case No.	Sex	Age (Yrs.)	Diagnosis	Total Dose of Dextran Sulphate (Units)	Oral Anticoagulant	Duration of Anticoagulant Therapy (Days)	Alopecia	Remarks
16	M	58	Persistent angina	30,000	Ethyl biscoumacetate	17	+	—
17	M	62	Thrombosis of I.V.C.	30,000	,,	21	—	—
18	M	42	Myocardial infarction	25,000	,,	2	—	Haematemesis after 2 days. Previous history of dyspepsia
19	M	52	,, ,,	25,000	,,	20	—	Treated with dextran sulphate again 9 months later (Case 8, Table I)
20	M	50	,, ,,	25,000	Phenindione	24	—	—
21	M	42	Venous thrombosis of leg and pulmonary embolism	20,000	,,	18	+	—
22	M	53	Myocardial infarction	15,000	,,	28	—	—
23	M	60	,, ,,	15,000	,,	28	—	—
24	M	50	,, ,,	15,000	,,	29	—	—
25	M	56	,, ,,	15,000	,,	23	—	—
26	F	45	Pulmonary embolism	15,000	,,	10	—	—
27	M	55	Venous thrombosis of leg	15,000	,,	11	—	Bronchial carcinoma

in two of these patients, both of whom subsequently developed a severe degree of alopecia (Figs. 2 and 3). In the other two, of whom one suffered alopecia and the other developed changes in the nails without alopecia, no significant change occurred in the platelet count during treatment with dextran sulphate.

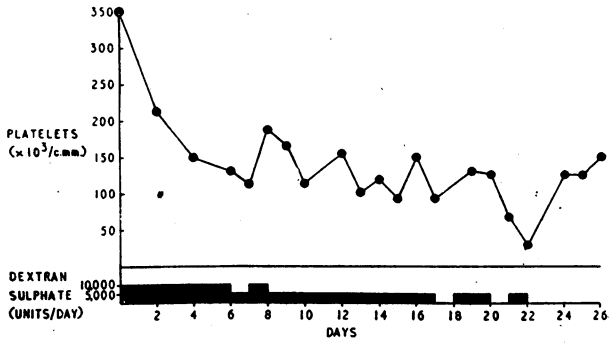

FIG. 2.—Platelets in peripheral blood during and after treatment with dextran sulphate in a case of myocardial infarction. Severe alopecia developed four weeks after stopping administration of dextran sulphate.

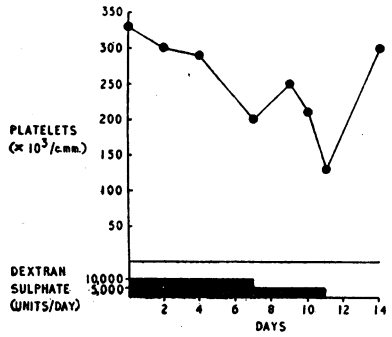

FIG. 3.—Platelets in peripheral blood during and after treatment with dextran sulphate, which was stopped after 11 days because of the development of diarrhoea. Severe alopecia occurred three weeks after the end of treatment.

Single platelet counts were performed 3 to 15 days after starting treatment in four other patients, two of whom subsequently developed alopecia. These platelet counts were all in the range of 200,000–350,000, so that thrombocytopenia was not detected during therapy.

Dextran Sulphate—Total Dose Less Than 40,000 Units

In the second group of 12 patients who received less than 40,000 units of dextran sulphate in addition to ethylbiscoumacetate or phenindione, two reported a mild loss of hair one to two months after the end of anticoagulant treatment. In both cases the hair loss was very mild and quite unlike the severe loss which occurred in patients of the first group.

Heparin and Oral Anticoagulant

Of the 60 patients treated with heparin and a coumarin drug, three reported loss of hair (Table III) and Case III had an extensive erythematous eruption while in hospital, suspected, but not proved, to be due to sensitization to phenindione. The loss of hair in this case occurred three weeks after discharge from hospital when the rash had entirely disappeared.

Discussion

Alopecia has been reported as a toxic effect of several heparin-like anticoagulants. Hirschboeck *et al.* (1954) found this complication in 19% of 68 patients treated with "treburon"; the loss of hair persisted for three to five months and involved mainly the scalp; axillary and pubic hair and eyebrows also became scanty in several patients. May (1951) reported transient alopecia in 70% of patients treated with "thrombocid." Dextran sulphate treatment has been previously reported to be followed by alopecia in 10% of cases (Donzelot *et al.*, 1955; Jeavons *et al.*, 1956). Using a higher dosage than most other workers, Hjort and Stormorken (1957) found that all 10 patients who received 20,000 units of dextran sulphate daily for 10 days suffered loss of hair. We observed severe alopecia in 8 out of 15 patients who had been followed up for at least three months after receiving 90,000 or more units of dextran sulphate; in three of these cases alopecia was not apparent until two months after the end of treatment. The lower incidence of alopecia reported by some other workers with dextran sulphate may be due partly to smaller dosage (Donzelot *et al.*, 1955) and partly to inadequate follow-up, as it was not at first realized that a latent period of two months might elapse between treatment and loss of hair (Jeavons *et al.*, 1956). The incidence of alopecia is much less when a smaller dose of dextran sulphate is given, and in the present study only 2 out of 12 patients receiving less than 40,000 units of dextran sulphate, along with a coumarin anticoagulant, developed mild alopecia. With treburon, Hirschboeck *et al.* (1954) found that the occurrence of alopecia appeared to bear no relationship to the total dose.

We also report diarrhoea in 4 out of 15 patients receiving at least 90,000 units of dextran sulphate; in two of these cases the diarrhoea was severe and was associated with the passage of blood in the stools. This has also been reported with treburon (Hirschboeck *et al.*, 1954).

Brittle and ridged finger-nails were observed in four patients treated with dextran sulphate, in three of whom severe alopecia also occurred. The only previous reports of such changes in the nails with heparin-like substances have been of one patient treated with treburon (Hirschboeck *et al.*, 1954) and another with dextran sulphate (Hjort and Stormorken, 1957).

There have been several accounts of alopecia occurring as a toxic effect of heparin, but estimates of the frequency of this complication have varied greatly. Merz (1950) reported alopecia in 54–66% of obstetrical and gynaecological cases treated with heparin; it affected the whole scalp but recovered spontaneously. Fischer *et al.* (1953) found that some degree of loss of hair occurred in 70% of patients who had been treated with a combination of heparin and a coumarin anticoagulant. They also reported that 30–40% of patients treated with coumarin drugs alone develop some loss of hair, and this appears to be the only report of alopecia occurring after coumarin drugs alone. Engelberg *et al.* (1956) gave 200 mg. of heparin subcutaneously twice weekly to 105 patients for 2 to 27 months and reported four cases of mild or moderate alopecia. Single cases of alopecia following heparin therapy have been reported by Plancherel (1952) and by Hirschboeck *et al.* (1954). On the other hand, various reviews of the actions

TABLE III.—*Details of Three Patients in whom Loss of Hair Occurred after Treatment with Heparin and Ethylbiscoumacetate or Phenindione*

Case No.	Sex	Age (Yrs.)	Diagnosis	Total Dose of Anticoagulant Drugs	Duration of Anticoagulant Treatment (Days)	Time from End of Treatment to Appearance of Alopecia (Weeks)	Type of Alopecia
I	M	42	Myocardial infarction	Heparin—20,000 units i.v. Ethylbiscoumacetate—8,000 mg.	21	3	Scalp only; mild diffuse loss of hair
II	M	47	,,	Heparin—30,000 units i.v. Ethylbiscoumacetate—8,350 mg.	23	4	Scalp only; marked diffuse loss of hair
III	M	65	,,	Heparin—40,000 units i.v. Phenindione—1,200 mg.	21	9	,, ,, ,,

and uses of heparin have contained no reference to the occurrence of alopecia (Jorpes, 1946, 1950; Best and Jaques, 1948; Duff *et al.*, 1951).

Wright (1953), in discussing the uses and toxic effects of anticoagulant drugs, did not mention alopecia with heparin, although stating that this complication occurs with the other sulphated polysaccharide anticoagulants, treburon and "paritol." De Takats (1953) stated that he had treated many hundreds of patients with heparin without observing alopecia, and suggested an impurity in some preparations as the cause. The latent period between treatment and obvious effect on hair, which is one to four months (Merz, 1950), may explain why some cases of alopecia have not been observed, but this is not likely to account for the big discrepancies in its reported incidence. It is more likely that a large total dose given during a period of a few weeks is the most important factor in the production of alopecia by heparin, as we have shown to be the case with dextran sulphate. We found that only 3 out of 60 patients treated with heparin and a coumarin-like anticoagulant developed alopecia. Merz (1950), in reporting that over 50% of patients treated with heparin developed alopecia, was referring mainly to treatment with heparin alone for several days or weeks, so that the total dosage was much greater than in the usual current practice of giving heparin for only 24 to 48 hours. It is probable that the incidence of alopecia with dextran sulphate is not any greater than with heparin in the same total dose.

Heparin causes a transient but profound decrease in circulating platelets when injected intravenously in dogs (Copley and Robb, 1941; Fidlar and Jaques, 1948), but not in man (Quick *et al.*, 1948). Plancherel (1952), however, found a reduction in platelets in 13 out of 30 cases during treatment with a long-acting preparation of heparin. Walton (1953) suggested that where heparin had been shown to cause reduction in platelets in man the effect was due to contamination with chondroitin sulphate of larger molecular weight than heparin. Several synthetic sulphated polysaccharides cause agglutination of platelets *in vitro* (Astrup, 1953) and when injected intravenously in rabbits (Piper, 1945). Dextran sulphate, of molecular weight about 7,500, does not cause agglutination of platelets following a single intravenous injection in rabbits (Walton, 1954; Astrup *et al.*, 1955). Hjort and Stormorken (1957) found that a significant decrease in circulating platelets occurred in man during treatment with repeated injections of dextran sulphate. We found that in two out of four patients in whom repeated counts of platelets were made during treatment with dextran sulphate there was a reduction in platelets occurring over several days, in one case reaching 30,000/c.mm. after 22 days. This is unlike the sudden and transient fall in platelet count occurring in animals after injection of some sulphated polysaccharides. The mechanism of platelet depression in these two patients is so far unexplained, but it is of interest that both subsequently developed severe alopecia.

The high incidence of alopecia, the occurrence of severe diarrhoea in some cases, and the possibility of a profound reduction in platelets in at least a few cases make treatment with dextran sulphate in high dosage clearly undesirable. In spite of the advantage of good control of clotting-time with infrequent injections, it is now clear that, when given in a total dose of more than 90,000 units, toxicity occurs too often. We have not observed any toxic effects when the total dose is less than 40,000 units; thus 5,000 units of dextran sulphate intravenously eight-hourly for 24 to 48 hours appears suitable as an alternative to heparin to cover the period until an oral anticoagulant becomes effective.

The mechanism by which dextran sulphate produces its effect on hair growth is unknown, but it possibly interferes with the metabolism of the naturally occurring sulphated polysaccharides or the sulphur-containing amino-acids. This problem is being investigated.

It is of great interest that the toxic effects of dextran sulphate—namely, alopecia, diarrhoea, thrombocytopenia, anorexia—are similar to some of the effects of whole-body irradiation, and of nitrogen mustards, colchicine, and other antimitotic substances, as well as of the folic acid antagonists. It has been shown that heparin itself has an antimitotic action (Heilbrunn and Wilson, 1949), and it is probable that dextran sulphate is similar in this respect. Furthermore, a heparin-like substance may be present in the blood following therapeutic doses of nitrogen mustards in man (Jacobson *et al.*, 1948) and after whole-body irradiation in animals (Allen and Jacobson, 1947). It has been suggested that some of the effects of irradiation may be due to the liberation into the blood of a toxic substance. Indeed, Van Dyke and Huff (1949) showed that irradiation of one member of a pair of parabiotically united rats produced loss of hair in both members of the pair. The production of alopecia by dextran sulphate may be only one aspect of a more general and fundamental action of the drug.

Summary

Severe alopecia occurred in 8 out of 15 patients treated with the anticoagulant drug dextran sulphate when the total dose was 90,000 or more units. Less than 40,000 units of dextran sulphate given with a coumarin anticoagulant produced mild loss of hair in 2 out of 12 patients.

Of 60 patients treated with heparin and a coumarin anticoagulant, three reported mild or moderate loss of hair following therapy.

Diarrhoea and depression of the platelet count were also noted in a few patients receiving a large total dose of dextran sulphate.

Previous reports of alopecia following anticoagulant treatment are reviewed.

All the patients treated with dextran sulphate were under the care of Professor G. M. Wilson, to whom we are grateful for advice and criticism. We thank Dr. T. E. Gumpert, Dr. A. W. D. Leishman, and Dr. R. S. Weetch for permission to study patients who had been under their care; Dr. E. K. Blackburn and the staff of the department of haematology, Royal Infirmary, Sheffield, who performed the platelet counts; Dr. K. Hardy, medical superintendent, Wharncliffe Hospital, for assistance in tracing case records; and Glaxo Laboratories Ltd., who supplied the dextran sulphate.

REFERENCES

Allen, J. G., and Jacobson, L. O. (1947). *Science*, **105**, 388.
Astrup, T. (1953). *Scand. J. clin. Lab. Invest.*, **5**, 137.
—— Flyger, H. H. K., and Gormsen, J. (1955). Ibid., **7**, 204.
Best, C. H., and Jaques, L. B. (1948). *Ann. N.Y. Acad. Sci.*, **49**, 501.
Cohen, H., and Tudhope, G. R. (1956). *Brit. med. J.*, **2**, 1023.
Copley, A. L., and Robb, T. P. (1941). *Amer. J. Physiol.*, **133**, 248.
de Takats, G. (1953). *Surgery*, **34**, 985.
Donzelot, E., Kaufmann, H., and Dauzier, G. (1955). *Sem. Hôp. Paris*, **31**, 1475.
Duff, I. F., Linman, J. W., and Birch, R. (1951). *Surg. Gynec. Obstet.*, **93**, 343.
Engelberg, H., Kuhn, R., and Steinman, M. (1956). *Circulation*, **13**, 489.
Fidlar, E., and Jaques, L. B. (1948). *J. Lab. clin. Med.*, **33**, 1410.
Fischer, R., Bircher, J., and Reich, T. (1953). *Schweiz. med. Wschr.*, **83**, 509.
Heilbrunn, L. V., and Wilson, W. L. (1949). *Proc. Soc. exp. Biol. (N.Y.)*, **70**, 179.
Hirschboeck, J. S., Madison, F. W., and Pisciotta, A. V. (1954). *Amer. J. med. Sci.*, **227**, 279.
Hjort, P., and Stormorken, H. (1957). *Scand. J. clin. Lab. Invest.*, **9**, Suppl. 29.
Jacobson, L. O., Marks, E. K., Gaston, E., Allen, J. G., and Block, M. H. (1948). *J. Lab. clin. Med.*, **33**, 1566.
Jeavons, S. M., Walton, K. W., and Ricketts, C. R. (1956). *Brit. med. J.*, **2**, 1016.
Jorpes, J. E. (1946). *Heparin in the Treatment of Thrombosis*, 2nd ed. Oxford Univ. Press, London.
—— (1950). *Acta chir. scand.*, Suppl. 149.
May, R. (1951). *Münch. med. Wschr.*, **93**, 1419.
Merz, W. R. (1950). *Gynaecologia (Basel)*, **130**, Suppl.
Piper, J. (1945). *Acta physiol. scand.*, **9**, 28.
Plancherel, P. (1952). *Z. klin. Med.*, **150**, 213.
Quick, A. J., Shanberge, J. N., and Stefanini, M. (1948). *J. Lab. clin. Med.*, **33**, 1424.
Ricketts, C. R. (1952). *Biochem. J.*, **51**, 129.
—— Walton, K. W., van Leuven, B. D., Birbeck, A., Brown, A., Kennedy, A. C., and Burt, C. C. (1953). *Lancet*, **2**, 1004.
Van Dyke, D. C., and Huff, R. L. (1949). *Proc. Soc. exp. Biol. (N.Y.)*, **72**, 266.
Walton, K. W. (1952). *Brit. J. Pharmacol.*, **7**, 370.
—— (1953). Ibid., **8**, 340.
—— (1954). Ibid., **9**, 1.
Wright, I. S. (1953). *Amer. J. Med.*, **14**, 720.