Thyroid Function Tests in Pendred's Syndrome

Subject No.	Serum P.B.I. ($\mu\text{g}/100\text{ ml}$)	Serum Thyopac-3	Free Thyroxine Index	Serum Thyroxine ($\mu\text{g}/100\text{ ml}$)	Serum Triiodothyronine (ng/ml)	Potassium Perchlorate Test Discharge as % of Max. Uptake	Circulating Thyroid Antibodies	TSH Released in Response to TRH Test ($\mu\text{U}/\text{ml}$)		
								0 mins	20 mins	60 mins
II 7	3.2	119	2.7	3.7	1.91	50	0	5.6	49	33.5
II 6	6.2	116	5.3	6.4	1.98	40	0	3.0	34	22.0
II 9	5.8	126	4.6	6.9	2.14	38.8	0	4.9	32	24.5
Mean normal values (95% confidence limits)	5.7 (3.1-8.3)	106 (92-120)	5.3 (2.5-9.0)	8.2 (4.4-12.0)	1.26 (0.79-1.73)	—	0	(<0.5-4.0)*	(6.5-20.5)*	(4.0-15.6)*

*Normal values for men and women derived from Ormston *et al.* (1971).

Results

The results of the thyroid function tests in the three affected members of the family and in controls are shown in the table. Serum T-3 was raised and the perchlorate test was positive in all the subjects. No circulating thyroid antibodies were found. Basal TSH levels were minimally raised in two subjects and the TSH response to TRH was exaggerated in all of them.

Discussion

The three siblings were clearly suffering from Pendred's syndrome. They had goitres, deaf mutism, and a thyroid organification defect indicated by the positive perchlorate discharge. All showed an unusual pattern of retinal pigmentation, an association not previously reported. They were clinically euthyroid and though the serum free thyroxine indices were in the normal range the increase in basal TSH and exaggerated response to TRH implied a suboptimal concentration of circulating thyroid hormone. The serum T-3 concentration was raised in all three subjects (but not in the unaffected relatives) and we assume that the increase was the result of increased TSH stimulation and maintained the euthyroid state. Preferential production of T-3 to maintain the euthyroid state has been reported in subjects with endemic goitre (Kochupillai *et al.*, 1973), after treatment with radioiodine, after pro-

pylthiouracil therapy (Sterling, 1970), and in the early stages of thyroid failure associated with autoimmune thyroid disease (Evered *et al.*, 1973). Probably an enhanced production of T-3 in these situations compensates for reduced T-4 production in subjects with a diminished intrathyroidal iodine pool. It seems likely that a similar situation occurs in subjects with Pendred's syndrome, though the possibility of increased peripheral conversion of T-4 to T-3 has not been excluded.

This work was supported by grants from the Wellcome Trust, the Medical Research Council, and the Scientific Research Council of Spain. We acknowledge the technical help of Mr. D. Weightman and Mrs. E. Green, and the help of the Departments of Clinical Biochemistry and Medical Physics.

References

- Burrow, G. N., Spaulding, S. W., Alexander, N. M., and Bower, B. (1972). *Israel Journal of Medical Sciences*, 8, 11.
 Evered, D. C., Ormston, B. J., Smith, P. A., Hall, R., and Bird, T. (1973). *British Medical Journal*, 1, 657.
 Hall, R., Amos, J., and Ormston, B. J. (1971). *British Medical Journal*, 1, 582.
 Hesch, R. D., and Evered, D. C. (1973). *British Medical Journal*, 1, 582.
 Kochupillai, N., *et al.* (1973). *Lancet*, 2, 1023.
 Morgans, M. E., and Trotter, W. R. (1958). *Lancet*, 1, 607.
 Ormston, B. J., Garry, R., Cryer, R. J., Besser, G. M., and Hall, R. (1971). *Lancet*, 2, 10.
 Pendred, V. (1896). *Lancet*, 2, 532.
 Sterling, K. (1970). *Recent Progress in Hormone Research*, 26, 249.

PRELIMINARY COMMUNICATIONS

Heparin Prophylaxis against Fatal Postoperative Pulmonary Embolism*

SHANTI SAGAR

British Medical Journal, 1974, 2, 153-154

Summary

Low-dose heparin prophylaxis against fatal pulmonary embolism has been studied in a random and prospective trial in 300 patients over the age of 50 who underwent major surgery. A dose of 5,000 IU mucous heparin sodium given two hours

preoperatively and for five days post operatively prevented fatal pulmonary embolism in all 156 patients so treated, whereas out of 144 patients in the unheparinized group 6 (4.2%) died of pulmonary embolism. This difference is statistically significant. There was no increase in operative or post-operative bleeding or in the formation of wound haematomas in the heparinized group.

Introduction

Prophylactic low-dose heparinization of patients over 50 years of age lowers the incidence of postoperative deep vein thrombosis (Sharnoff and De Blasio, 1970; Kakkar *et al.*, 1972). So far there is no evidence that prophylactic heparinization will reduce the incidence of postoperative fatal pulmonary embolism (*British Medical Journal*, 1973; Wessler and Thye Lin, 1973).

The factors responsible for venous thrombosis are thought to be stasis, intimal damage, and increased coagulability of the blood (Virchow, 1856; Browse, 1970). Pelvic venous pooling and intimal damage cannot be influenced with certainty, whereas the coagulability of the blood can be readily decreased. The operative period is regarded generally as the

*Based on a paper presented at the West Midlands Surgical Society Meeting at Birmingham on 27 October 1973.

most critical time for the development of "hypercoagulation" and the initiation of intravascular thrombosis (Flanc *et al.*, 1968; Sharnoff, 1973; Wessler and Thye Lin, 1973). Thus it is reasonable to suppose that if this state of hypercoagulability could be neutralized before intravascular coagulation is triggered off then less of the antithrombotic agent would be required than if therapy were begun after clotting had started. Activated factor X (thrombokinase) occupies a key position in the intrinsic and extrinsic coagulatory mechanisms and is activated by tissue damage. Heparin inhibits the conversion by thrombokinase of prothrombin to thrombin. Thus if heparin is administered before tissue trauma activates factor X low doses may be adequate in decreasing the state of coagulability, thereby preventing intravascular thrombus formation (De Takats, 1950; Lenggenger 1957; Kakkar *et al.*, 1971; Gordon-Smith *et al.*, 1972; Nicolaides *et al.*, 1972).

The object of this trial was to give heparin in small doses to reduce hypercoagulability without increasing operative or post-operative bleeding. The results have been assessed by evaluating the incidence of fatal pulmonary embolism found at necropsy.

Method

A prospective, controlled, random trial is being carried out at the North Staffordshire Hospital Centre to study the efficacy

TABLE I—Sex Distribution of Control and Heparinized Patients studied to Date

	Control Patients	Heparinized Patients	Total
Men	85	80	165
Women	59	76	135
Total	144	156	300

TABLE II—Operative Procedures carried out in the Two Groups of Patients

	Control Group	Heparinized Group	Total
Thoracic	33	35	68
Gastric	13	16	29
Biliary	20	19	39
Intestinal	17	18	35
Abdominoperineal resection	8	10	18
Laparotomy and palliation	16	17	33
Urological	4	5	9
Prostatic	7	9	16
Histis hernia	8	10	18
Miscellaneous	18	17	35
Total	144	156	300

TABLE III—Numbers and Causes of Postoperative Deaths in the Two Groups of Patients

	Control Group	Heparinized Group	Total
All causes	18	14	32
Pulmonary embolism	6	0	6

TABLE IV—Operative Procedures and Diagnoses in 6 Control Patients dying from Pulmonary Embolism and Comparison of Similar Cases

Operation	Diagnosis	Age	Sex	Day of Death Postoperatively	No. of Similar Cases	
					Control Group (n = 41)	Heparinized Group (n = 43)
Laparotomy and palliative surgery	Carcinoma of colon	60	F.	3	9	9
Laparotomy and palliative surgery	Carcinoma of stomach	73	F.	6	4	5
Hemicolectomy	Carcinoma of caecum	77	M.	9	4	5
Prostatectomy	Adenoma of prostate	65	M.	10	7	9
Lobectomy	Lung cyst	55	M.	10	3	5
Vagotomy and pyloroplasty	Chronic duodenal ulcer	67	F.	36	14	10

Efficacy of heparin prophylaxis: $\chi^2 = 4.78$; $P < 0.05$ (with Yates's correction).

of low-dose heparinization in preventing fatal pulmonary embolism. The patients are over 50 years who are due for elective major surgery. Four general surgeons, two thoracic surgeons, and one urological surgeon have agreed to let patients under their care participate in the trial. The patients are allocated at random either to the heparinized group or to the control group by using statistical tables. Each ward is supplied with heparin and forms. A separate chart records the administration of heparin and is signed by the nurse concerned.

A dose of 5,000 IU mucous heparin sodium (0.2 ml of 25,000 IU/ml) is injected subcutaneously with a 25-gauge needle two hours preoperatively and at 12-hour intervals post-operatively for five days.

Coagulation studies have been carried out in some patients to measure the degree of heparinization using the partial thromboplastin time, prothrombin index, and thrombin clotting time (Eika *et al.*, 1972) and thromboelastography (Marchall *et al.*, 1962). Blood samples are taken preoperatively and at two-hour intervals after the initial heparin injection for 12 hours. The injection sites are examined for haematoma formation during the postoperative period. All patients who die come to necropsy.

Results

Altogether 300 patients have been studied so far (tables I and II). When a patient is withdrawn because of a specific contra-indication or because a heparin injection has been missed, his form is reissued to the next patient on the register. Of the 300 patients studied 156 were heparinized (table I). There were 14 deaths in this group (table III). Of the 144 patients in the control group 18 died postoperatively, and in six of these pulmonary embolism was the cause of death. The remainder died of other complications such as cardiac failure, bronchopneumonia, peritonitis, and of carcinomatosis.

Of the six patients in the control group whose deaths were due to pulmonary embolism three had carcinoma (table IV). In two of these cases laparotomy and bypass palliation such as gastroenterostomy and ileocolic anastomosis had been carried out as metastases were found. The average age of these patients was 66 years and the mean postoperative time of death 12.3 days.

Since there were no deaths from pulmonary embolism in the heparinized group these results are statistically significant ($P < 0.05$ with Yates's correction). There were almost equal numbers of similar types of cases both in control group (41 patients) and in the heparinized group (43 patients), and hence the two groups were comparable (table III).

Discussion

Patients participating in this trial are selected on the basis of their age and the fact that they are to undergo elective major operations. Patients undergoing minor surgical procedures and endoscopy are excluded, as are open-heart and vascular cases where heparin is given intra-arterially during the operation (table II).

In 1972 at this centre the incidence of postoperative fatal pulmonary embolism in patients over the age of 50 was 1.35% (calculated from 1 800 necropsy reports). The incidence of fatal pulmonary embolism in this series was higher (2%), but this was because the patients constituted a high-risk group and included both the heparinized cases and the controls.

The dosage regimen had no apparent effect on clotting times. There was a variation of 5 to 20 seconds in the thrombin clotting time, which is within normal limits. Thromboelastographic recordings were well within the normal range. The peak plasma levels of heparin after the subcutaneous injection of 5 000 units were less than 0.013 IU/ml. (With conventional therapy the peak plasma level of heparin is 1.3 IU/ml; Kakkar *et al.*, 1971). Thus the circulating heparin levels were subclinical—that is, there was no evidence of increased operative or postoperative bleeding or wound haematoma formation—and thus safe.

When asked to comment on the degree of bleeding at operation the surgeons were unable to distinguish between the two groups. There was no increase in postoperative bleeding or wound haematoma formation. Two patients were withdrawn at the request of the surgeon because of a suspected increase in postoperative bleeding but coagulation studies showed nothing abnormal. Drainage measurements after abdominoperineal resections and thoracotomies did not show any significant difference between the two groups.

The mucous heparin sodium used in the trial is manufactured in the U.K. and is readily available. In previous studies calcium and sodium salts of heparin (lung) have been used (Sharnoff and De Blasio, 1970; Kakkar *et al.*, 1971; Kakkar *et al.*, 1972; Nicolaides *et al.*, 1972) and the advantages claimed were fewer local haematomas, and possibly longer-sustained levels in plasma. Haematoma formation at the site of injection was not a problem in this series and the results confirm that the sodium salt of mucous heparin works as effectively as calcium heparin and is much cheaper. The potential errors in a study of this kind arise mainly from the use of unstandardized methods—namely, the matching of patients

and variable factors such as surgical technique—and the use of other thromboembolic precautions. This is, however, a controlled random trial and statistically these factors will cancel one another out as the number of patients increases.

The clinical diagnosis of pulmonary embolism is often difficult and unreliable. Aids such as scanning, angiography, etc., are not without hazards or foolproof (Oakley 1970; Poulouse *et al.*, 1970). Hence evaluation of the efficacy of heparin prophylaxis is made at necropsy.

I am indebted to Mr. J. M. Sanderson and Mr. J. McKenzie Buchanan for their encouragement, guidance, and help in this project, and also to Mr. P. Beckett for his technical help; Dr. M. M. Koshi for associating with me in this project; Messrs. P. M. Higgins, W. Sewell, L. J. Lawson, I. G. Gray, and E. G. Brewin, who have allowed patients under their care to participate in this trial; the consultant pathologists for their necropsy reports; Mrs. R. McLean for her painstaking secretarial work; Miss Julia Massey for statistical advice; and, finally, but not least, the nursing staff and my junior colleagues for their help.

References

- ¹ *British Medical Journal*, 1973, 2, 1.
- ² Browse, N. L. (1970). *British Medical Journal*, 2, 780.
- ³ De Takats, G. (1950). *Journal of the American Medical Association*, 142, 527.
- ⁴ Eika, C., Godal, H. C., and Kierulf, P. (1972). *Lancet*, 2, 376.
- ⁵ Flanc, C., Kakkar, V. V., and Clarke, M. B., (1968). *British Journal of Surgery*, 55, 742.
- ⁶ Gordon-Smith, I. C., Grundy, D. J., Le Quesne, L. P., Newcombe, J. F., and Bramble, F. J. *Lancet*, 1, 1133.
- ⁷ Kakkar, V. V., *et al.* (1971). *Lancet*, 2, 669.
- ⁸ Kakkar, V. V., *et al.* (1972). *Lancet*, 2, 101.
- ⁹ Leggenhager, K. (1957). *Helvetica Chirurgica Acta*, 24, 316.
- ¹⁰ Marchall, G., Leroux, M. E., and Samama, R. M. (1962). *Atlas de Thrombodynamographie*. Paris, Service de Propagande.
- ¹¹ Nicolaides, A. N., *et al.* (1972). *Lancet*, 2, 890.
- ¹² Oakley, C. M. (1970). *British Medical Journal*, 2, 773.
- ¹³ Poulouse, K. P., *et al.* (1970). *British Journal of Surgery*, 57, 293.
- ¹⁴ Sharnoff, J. G. (1933). *Lancet*, 2, 1321.
- ¹⁵ Sharnoff, J. G., and De Blasio, G. (1970). *Lancet*, 2, 1006.
- ¹⁶ Virchow, R. L. (1856). *Gesammelte Abhandlungen zur Wissenschaftlichen Medizin*, p. 219. Frankfurt, Meidinger.

MEDICAL MEMORANDA

Myocarditis Complicating Q Fever

P. SHERIDAN, J. N. MACCAIG, R. J. C. HART

British Medical Journal, 1974, 2, 155-156

Cardiac involvement in Q fever is well recognized, the lesion being usually endocarditis (Evans *et al.*, 1959; Robson and Shimmin, 1959; Marmion *et al.*, 1960; Smith and Evans, 1960). Myocarditis complicating Q fever though mentioned in the European literature (Giroud and Goulon, 1953; Busila *et al.*, 1971), does not appear to be recorded in the English literature and is not listed in recent editions of standard textbooks. We describe here two such cases in which myocarditis was a prominent feature.

Royal Devon and Exeter Hospital, Southernhay, Exeter

P. SHERIDAN, M.B., M.R.C.P., Senior Registrar (Research) (Present address: Department of Medicine, Leeds (St. James's) University Hospital, Leeds LS9 7TF)

North Devon Infirmary, Barnstaple, Devon

J. N. MACCAIG, M.B., M.R.C.P., Consultant Physician

Public Health Laboratory, Church Lane, Heavitree, Exeter

R. J. C. HART, M.B., M.R.C.PATH., Consultant Virologist

Case 1

In April 1972 a 42-year-old motor mechanic was admitted to the Royal Devon and Exeter Hospital as an emergency case with chest pain and a provisional diagnosis of myocardial infarction. He lived and worked in the city. He drank pasteurized milk and rarely visited the countryside. His illness had begun four days previously with shivering and muscular aches. There were no respiratory symptoms and he had no headache. On the day of admission he experienced sudden, tight pain across the front of his chest radiating to the jaw and left scapular region. He sweated profusely. The pain was not related to posture or inspiration and lasted two hours. Temperature 39.5°C; pulse 90/min, regular; blood pressure 120/70 mm Hg. Examination of the heart and chest showed nothing abnormal.

In view of the prodromal symptoms steps were taken to exclude viral myocarditis. Investigations were: haemoglobin 13.6 g/100 ml; W.B.C. 8,600/mm³ (81% polymorphs); E.S.R. 91 mm in the first hour (Westergren); serum aspartate transferase 250 mU/ml (normal 10-50 mU/ml); and lactic acid dehydrogenase 430 mU/ml (normal 30-85 mU/ml). Chest x-ray changes were compatible with pneumonitis at the left base. Serial E.C.G. showed progressive changes compatible with acute myocardial damage inferolaterally (fig. 1). No virus was isolated from throat swab or faeces but *Coxiella burnetii* phase II complement fixation titres rose from 1/10 on the fourth day of the illness to 1/160 on the eighth day. Phase I titres were negative throughout.

The fever and symptoms settled after five days without treatment. The haematological and biochemical findings were normal by the sixth week. A year later he was in good health, having had no recurrence, and an E.C.G. was normal.