most important aspect for most patients, who in the present situation cannot expect to survive more than a few years and who may suffer the anguish of local recurrence before death.

The Working Party wishes to pay tribute to the generosity of the Nathan Trust, which provided considerable financial assistance. It is grateful to the Bone Tumour Panel of the British Empire Cancer Campaign for reviewing the histological material and to the department of morbid anatomy of the Institute of Orthopaedics (Dr. H. A. Sissons) for preparing the many histological sections concerned and arranging their circulation to the panel. Furthermore, the Working Party is deeply appreciative of the generous co-operation of the clinicians and pathologists in the centres which supplied information.

Reference

Mackenzie, A., Court Brown, W. M., Doll, R., and Sissons, H. A. (1961). *British Medical Journal*, 1, 1782.

Oestrogen as a Reticuloendothelial Stimulant in Patients with Cancer

C. J. MAGAREY, M. BAUM

British Medical Journal, 1971, 2, 367–370

Summary

Stimulation of reticuloendothelial activity may benefit patients with cancer. Oestrogenic compounds are known to stimulate reticuloendothelial phagocytic activity in animals and a similar effect is demonstrated in patients.

The depression of reticuloendothelial phagocytic activity which follows radiotheraphy in the treatment of cancer can be prevented by the simultaneous administration of stilboestrol. Possibly this could be associated with a more favourable response to therapy, and a controlled trial is needed to establish this.

Introduction

The reticuloendothelial system is important in the natural resistance of cancer patients to the spread of their tumours (Green *et al.*, 1967). Phagocytic activity in particular has been found to reflect this resistance (Magarey and Baum, 1970). But this activity is depressed by ionizing radiation or cytotoxic drugs used in the treatment of patients with cancer (Magarey and Baum, 1970). In animals the spread of tumours is increased by agents which depress reticuloendothelial phagocytic activity (Kondo and Moor, 1961; Reiner and Southam, 1966; Dao and Yogo, 1967; Rosenau and Moon, 1967). Conversely, agents which stimulate reticuloendothelial phagocytic activity reduce the spread of these tumours (Bradner and Clarke, 1959; Old *et al.*, 1961; Yamaguchi *et al.*, 1965; Halpern *et al.*, 1966; Woodruff and Boak, 1966). Such reticuloendothelial stimulants potentiate the antitumour effects of cytotoxic compounds (Sokoloff *et al.*, 1961; Martin *et al.*, 1964). So far, there have been few serious attempts to stimulate reticuloendothelial activity in humans with cancer, though Mathé (1969) claimed some success with B.C.G. in patients with leukaemia.

Oestrogens are potent stimulants of reticuloendothelial phagocytic activity in laboratory animals (Nicol, 1935; Biozzi *et al.*, 1957; Nicol *et al.*, 1964). They. like other reticuloendothelial stimulants, give some protection against the toxic effects of *x*-irradiation (Treadwell *et al.*, 1943; Mirand and Lasser, 1955) and cytotoxic compounds (Baum, 1967; Field *et al.*, 1967). Oestrogens have been used for years in the treatment of patients with breast or prostatic cancer, but their mode of action is not fully understood. Nicol *et al.* (1952) provided histological evidence that macrophage activity may be involved in the response of prostatic cancer to oestrogens, but there have been few experimental studies of the effects of oestrogen on the host response to tumour. There have been no such studies in man, though oestrogens are less toxic than the reticuloendothelial stimulants which have so far been considered for use in patients with cancer.

The following investigations were undertaken to study the effects of several oestrogens on the reticuloendothelial phagocytic activity in patients with cancer and in patients without malignant disease and, in addition, the effect of combining stilboestrol with radiotherapy in the treatment of patients with cancer.

Patients and Methods

Sixty-three patients volunteered for this study (Table I). Fifteen who had malignant disease and 33 who had no malignant disease, all of whom were in good general health, were given oestrogen. Another seven patients received stilboestrol while undergoing radiotherapy. These patients received no other specific treatment during the investigation except promethazine or perphenazine to prevent the nausea sometimes produced by oestrogen. The other eight patients without malignant disease acted as controls and took promethazine or perphenazine but no oestrogen. The results obtained in the patients undergoing radiotherapy have been compared with those obtained in 22 patients receiving similar radiotherapy without stilboestrol (Magarey and Baum, 1970).

The oestrogens were taken orally. Stilboestrol was taken in three dose ranges (1 mg three times daily, 5-10 mg three times daily, or 25 mg four times daily). Ethinyloestradiol was taken in two dosages (0·1 or 1 mg three times daily). Oestriol was

TABLE I—*Patients in Study*

Without malignant disease		
Receiving promethazine or perphenazine		8
Receiving oestrogen	Six weeks after hysterectomy	32
	Benign warts	1
With malignant disease		
Receiving oestrogen	Carcinoma prostate	8
	Carcinoma breast	5
	Carcinoma ovary	2
Stilboestrol plus radiotherapy	Carcinoma bronchus	4
	Carcinoma bladder	3

Department of Surgery, King's College Hospital Medical School, London S.E.5

C. J. MAGAREY, F.R.C.S., F.R.C.S.ED., Research Fellow (Present appointment: Surgical Registrar, Royal United Hospital, Bath)
M. BAUM, F.R.C.S., Lecturer

taken in one dosage (0·5 mg three times daily). Reticuloendothelial phagocytic activity was measured in the patients by the method described by Magarey (1970).

Microaggregated albumin labelled with ^{125}I was injected intravenously in a dose of 5 mg/kg body weight. Blood samples were withdrawn from 5 to 12 minutes later. The radioactivity was measured in an automatic well type iodide crystal scintillation counter. The logarithm of the counts of radioactivity plotted against time was linear, and the slope, calculated by the method of least squares, was the clearance rate of the aggregate from the blood stream by phagocytosis in the hepatic sinusoidal macrophages (Magarey, 1970). Since this was a small negative number it was multiplied by minus 100 to give the phagocytic index K. The K value was measured in each patient before and each week during treatment. In each individual the same batch of aggregate was used throughout. The difference between the first and each subsequent K value was calculated and expressed as the ΔK value. The mean of the ΔK values obtained in the patients in each treatment group was calculated and its significance determined with Student's *t* test.

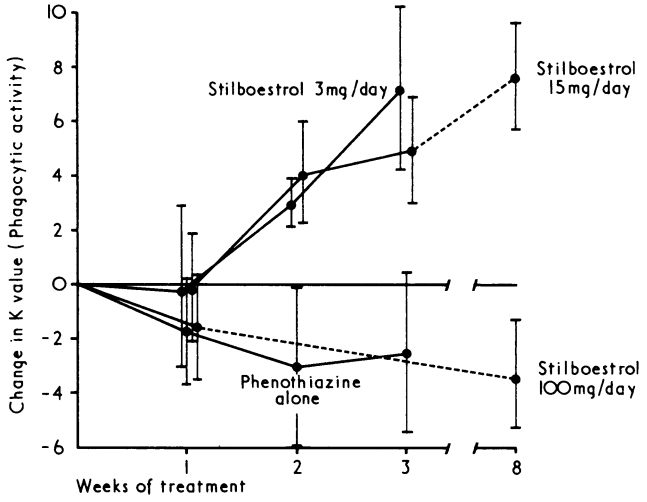

FIG. 1—Effect of stilboestrol on human phagocytic activity. Phagocytic activity, expressed as K value, was measured in volunteers and patients with inoperable breast or prostatic cancer receiving stilboestrol 3, 15, or 100 mg a day, or a phenothiazine without stilboestrol. In each patient the differences between the K value obtained before treatment and those obtained during treatment were calculated and expressed as the ΔK value. The mean of the ΔK values in each group of patients within each week of treatment is shown with marks of one standard error.

Results

EFFECT OF STILBOESTROL

The means of the ΔK values obtained during the administration of stilboestrol are presented in Table II and Fig. 1. For comparison, the mean ΔK values obtained in the patients receiving a phenothiazine but no oestrogen are given. Their K values were not affected. There was a significant increase in K value in the patients taking 3 mg of stilboestrol a day for three weeks, and in those taking 15 mg a day for two or for three weeks. Only a small number of patients received 100 mg a day, but there was no suggestion of an increase in their K values.

The patients receiving 15 mg of stilboestrol daily are grouped according to whether they had malignant disease or not. A rise in K value occurred in both groups. Two of the three with carcinoma of the breast improved clinically as a result of this treatment, but neither of the two with carcinoma of the ovary appeared clinically to be affected.

EFFECT OF OTHER OESTROGENS

The means of ΔK values obtained in the patients who received ethinyloestradiol, 0·3 or 3 mg a day, or oestriol, 1·5 mg a day, are also shown in Table II and Fig. 2. None of the mean ΔK values were significant to the level of 95% probability.

EFFECT OF STILBOESTROL WITH IRRADIATON

The ΔK values obtained in the patients who received stilboestrol with their irradiation have been compared with those obtained in other patients who received similar irradiation to the chest or pelvis but no stilboestrol (Magarey and Baum, 1970).

The means of the ΔK values obtained within each dose range are presented in Table III and Fig. 3. There was an increase in K value in the patients receiving stilboestrol while undergoing irradiation. This was more pronounced in the patients with bladder tumours, and within the mid-pelvic dose range of 2,000-4,000 rad the difference in ΔK values between those receiving stilboestrol and those not receiving stilboestrol was significant ($P<0.05$). The differences did not attain signifi-

TABLE II—*Effect of Oestrogen on Phagocytosis in Humans. Mean ΔK Values*

Time of Treatment	Phenothiazine	Stilboestrol 3 mg	Stilboestrol 15 mg	Stilboestrol 15 mg Cancer	Stilboestrol 15 mg Non-Cancer	Stilboestrol 100 mg	Ethinyl-oestradiol 0·3 mg	Ethinyl-oestradiol 3 mg	Oestriol 1·5 mg
First week ..	(7) −1·7±2	(7) −0·1±3	(14) −0·1±2	(3) + 2·7±3	(11) −0·6±2	(5) −1·6±2	(5) +2·4±1	(5) −1·2±3	(6) −2·2±3
Second week ..	(5) −3·0±3	(5) +3·0±1	(17) +4·1±2*	(6) + 5·2±4	(11) +3·5±2		(5) +4·2±4	(2) +5·0±4	(3) −0·7±5
Third week ..	(4) −2·5±3	(5) +7·2±3	(9) +5·0±2*	(3) + 5·7±2	(6) +5·8±3		(4) +1·5±2	(3) −0·7±3	(4) −1·0±2
Third and subsequent weeks			(13) +7·7±2†	(6) +10·2±4	(7) +5·6±3	(3) −3·3±2			

Numbers of cases are given in parentheses.
*P<0·05 †P<0·01

TABLE III—*Effect of Stilboestrol (15 mg a day) combined with Radiotherapy on Phagocytosis in Humans. Mean ΔK Values.*

Dose of x-Irradiation (rads)	Pelvic Irradiation				Chest Irradiation			
	Alone		Stilboestrol		Alone		Stilboestrol	
<1,000	(4)	+1·0±3	(3)	+2·0±11	(14)	+0·6±2	(4)	+5·5±5
1,000-2,000	(7)	−6·1±2*	(2)	−3·5±1	(13)	−1·8±2	(5)	+3·8±1*
2,000-3,000	(8)	−7·3±3*§	(6)	+6·8±2*§	(12)	−1·5±3	(3)	+3·3±7
3,000-4,000								
>4,000	(7)	−9·1±4*	(6)	+0·3±4	(10)	−2·3±3	(1)	+13
All results >1,000 rad..	(22)	−7·5±2†‖	(14)	+3·5±2‖	(35)	−1·9±1·6‡	(9)	+4·7±2*‡
3 weeks after therapy ..	(3)	−4·3±2	(3)	+2·7±4	(9)	+2·2±4	(2)	−5·1

Number of cases is given in parentheses.
Significance of mean ΔK values: *P<0·05 †P<0·001
Significance of difference between means: ‡P<0·05 §P<0·01 ‖P<0·001

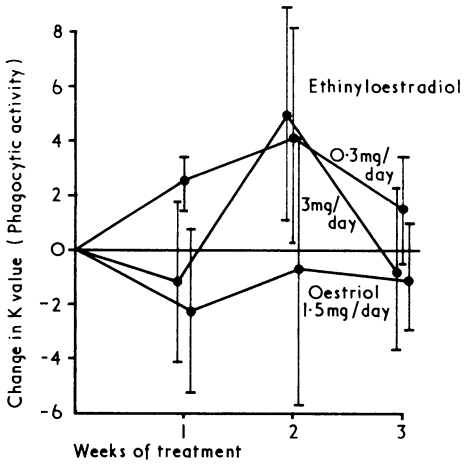

FIG. 2—Effect of steroid oestrogens on human phagocytic activity. The mean changes in phagocytic activity expressed as K value are shown in the same way as in Fig. 1. The volunteers and patients received either ethinyloestradiol 0·3 or 3 mg a day or oestriol 1·5 mg a day.

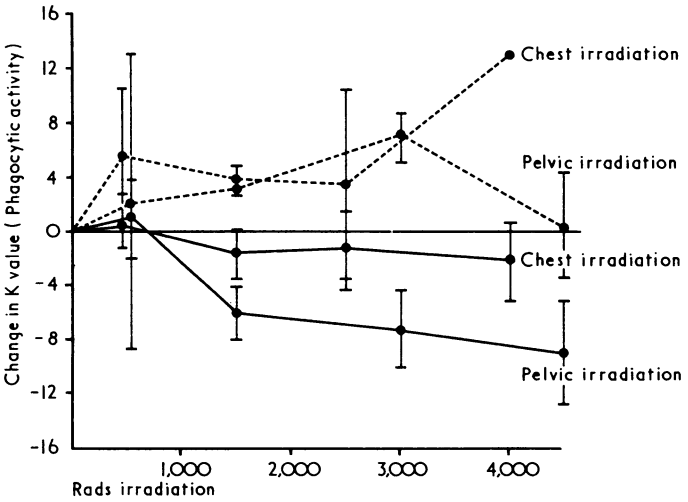

FIG. 3—Effect of stilboestrol combined with radiotherapy on phagocytic activity in humans. Phagocytic activity, expressed as K value, was measured in patients with carcinoma of the bronchus, bladder, or ovary undergoing radiotherapy to the chest or pelvis respectively. Many of the patients underwent radiotherapy alone (solid lines). Other patients received stilboestrol, 15 mg a day, with their radiotherapy (interrupted lines). The mean changes in phagocytic activity within each range of irradiation dose are shown in the same way as in Fig. 1.

cance in the other dose ranges but when all ΔK values obtained after 1,000 rad (mid-pelvic dose) were considered, the difference between the groups was highly significant ($P<0.001$). Few results were obtained in the higher dose ranges of chest irradation with stilboestrol since one patient did not attend to complete his radiotherapy and it was necessary to stop the stilboestrol in another because of nausea. The differences in ΔK values between those receiving stilboestrol and those not receiving stilboestrol during chest irradiation were not, therefore, significant within each dose range, but when all the ΔK values obtained after 1,000 rad (mid-mediastinal dose) were considered the difference between the groups was significant ($P<0.05$).

The tumours regressed in each of the seven patients who received stilboestrol with their radiotherapy, but regression occurred in only 12 of the 22 patients who did not receive stilboestrol. Too few patients were studied, however, for an adequate statistical analysis to be made of these clinical responses.

Discussion

A rise in reticuloendothelial phagocytic activity has been found to occur in patients taking stilboestrol orally in doses of from 3 to 30 mg a day. The larger dose was effective after a week and the smaller after two weeks. Both patients with cancer and patients without malignant disease were affected. Very high doses of stilboestrol, 100 mg a day, appeared to produce less or no effect. This biphasic effect has been found in the case of other agents acting on reticuloendothelial phagocytic activity (Sokoloff *et al.*, 1961; Weiss *et al.*, 1961; Draper, 1962; Nicol *et al.*, 1965).

Two steroid oestrogens have been studied in addition, oestriol (1·5 mg a day) and ethinyloestradiol (0·3 and 3 mg a day). There was no evidence that oestriol, in this dose, stimulated reticuloendothelial phagocytic activity in humans, and ethinyloestradiol appeared to be a less effective stimulant of reticuloendothelial activity than was stilboestrol, in the doses used. Since stilboestrol was found to be a satisfactory reticuloendothelial stimulant further studies were confined to this compound.

Reticuloendothelial reactivity is higher in female rats and mice than in males (Halpern *et al.*, 1960; Batchelor and Chapman, 1965; Graff *et al.*, 1969) and varies with the oestrus cycle (Nicol and Vernon-Roberts, 1959). This may account for the relative resistance of female mice to tumours (Old *et al.*, 1961; Thunold, 1967; Bates, 1968). Ashley (1969) presented data that showed a lower incidence of tumours in women than in men, if lesions of the dissimilar sex organs and of the lung were excluded. Perhaps women have a greater resistance to the development of malignant disease because of a naturally heightened reticuloendothelial activity.

In the previous study we found that a depression occurred in reticuloendothelial phagocytic activity in patients with cancer undergoing radiotherapy to the mediastinum or pelvis (Magarey and Baum, 1970). This depression was associated with a poor clinical response to treatment and may have reflected damage to the natural resistance of the patients to their tumours. In the present study no depression occurred in reticuloendothelial phagocytic activity in the patients who received stilboestrol while undergoing comparable radiotherapy. The tumours in each of the patients receiving stilboestrol regressed during treatment. This effect could not be adequately studied statistically but was highly suggestive, and is worth pursuing with a properly designed trial.

Stimulation of reticuloendothelial activity alone has rarely produced regression of established tumour masses in experimental animals (Old and Boyse, 1964). The host defences appear to be overwhelmed in the presence of a large bulk of tumour (Fairley, 1969), so the ablation of the main mass of a tumour by conventional means is likely to remain necessary. Nevertheless, if this damages the natural defences against the tumour, the outgrowth of distant metastases may be accelerated. Radiotherapy and cytotoxic chemotherapy depress reticuloendothelial phagocytic activity in patients with cancer (Magarey and Baum, 1970) and may, therefore, produce such acceleration of tumour growth. Reticuloendothelial stimulants provide some protection from the toxic effects of these agents and may, therefore, protect the natural defences against tumours. A combination of radiotherapy and cytotoxic chemotherapy with non-specific reticuloendothelial stimulation is likely, therefore, to provide a more effective means of treatment of cancer. This has been shown experimentally (Sokoloff *et al.*, 1961; Martin *et al.*, 1961, 1964) and in patients with acute leukaemia (Mathé, 1969).

In this study stilboestrol has been found to stimulate reticuloendothelial phagocytic activity in humans and to prevent the depression in reticuloendothelial phagocytic activity associated with radiotherapy in patients with cancer. Oestrogen is less toxic than the other reticuloendothelial stimulants which have been recommended for use in humans with cancer, such as B.C.G. inoculation (Mathé, 1969) or *Corynebacterium parvum* administration (Woodruff and Boak, 1966).

This work was carried out during the tenure of Cancer Research Campaign Fellowships in the department of surgery, King's College Hospital.

Professor J. G. Murray and Mr. C. T. Howe gave encouragement and advice. Professor T. Nicol, Dr. B. Vernon-Roberts, and Dr. D. C. Quantock, of the department of anatomy, King's College, London, suggested the application of their technique using aggregated albumin prepared by the research department of Pfizer Ltd. The radioactive isotopes were handled by Mr. M. B. Clark. Dr. R. P. Knill-Jones advised on the statistical methods and provided computer programmes to assist with the calculations.

References

Ashley, D. J. B. (1969). *British Journal of Cancer*, **23**, 21.
Batchelor, J. R., and Chapman, B. A. (1965). *Immunology*, **9**, 553.
Bates, R. R. (1968). *Journal of the National Cancer Institute*, **41**, 559.
Baum, M. (1967). *British Journal of Surgery*, **54**, 229.
Biozzi, G., *et al.* (1957). *Comptes Rendus des Séances de la Société de Biologie et des ses Filiales*, **151**, 1326.
Bradner, W. T., and Clarke, D. A. (1959). *Cancer Research*, **19**, 673.
Dao, T. L., and Yogo, H. (1967). *Cancer (Philadelphia)*, **20**, 2020.
Draper, L. R. (1962). In *Ionising Radiations and Immune Processes*, ed. C. A. Leone, p. 221. New York, Gordon and Breach.
Fairley, G. H. (1969). *British Medical Journal*, **2**, 467.
Field, J. R., Ershoff, B. H., Dolendo, E., and Mireles, A. (1967). *Proceedings of the American Association for Cancer Research*, **8**, 17.
Graff, R. J., Lappé, M. A., and Snell, G. D. (1969). *Transplantation*, **7**, 105.
Green, H. N., Anthony, H. M., Baldwin, R. W., and Westrop, J. W. (1967). *An Immunological Approach to Cancer*. London, Butterworths.
Halpern, B. N., Stiffel, G., Biozzi, G., and Mouton, D. (1960). *Comptes Rendus des Seances de la Societe de Biologie et des ses Filiales*, **154**, 1994.
Halpern, B. N.. Biozzi, G., Stiffel, C., and Mouton, D. (1966). *Nature*, **212**, 853.
Kondo, T., and Moore, G. E. (1961). *Cancer Research*, **21**, 1396.
Lancet, 1968, **1**, 1298.
Magarey, C. J. (1970). Thesis submitted to the University of Sydney for the Degree of Master of Surgery.
Magarey, C. J., and Baum, M. (1970). *British Journal of Surgery*, **57**, 748.
Martin, D. S., Fugmann, R. A., and Hayworth, P. (1961). *Journal of the American Medical Association*, **178**, 723.
Martin, D. S., Hayworth, P., Fugmann, R. A., English, R., and McNeill, H. W. (1964). *Cancer Research*, **24**, 652.
Mathé, G. (1969). *British Medical Journal*, **4**, 7.
Mirand, E. A., and Lasser, E. C. (1955). *Experimental Medicine and Surgery*, **13**, 234.
Nicol, T. (1935). *Transactions of the Royal Society of Edinburgh*, **58**, 449.
Nicol, T., Helmy, I. D., and Abon-Zikry, A. (1952). *British Journal of Surgery*, **40**, 166.
Nicol, T., and Vernon-Roberts, B. (1959). *Journal of the Reticuloendothelial Society*, **2**, 15.
Nicol, T., Bilbey, D. L. J., Charles, L. M., Cordingley, J. L., and Vernon-Roberts, B. (1964). *Journal of Endocrinology*, **30**, 277.
Nicol, T., Vernon-Roberts, B., and Quantock, D. C. (1965). *Journal of Endocrinology*, **33**, 365.
Old, L. J., Benacerraf, B., Clarke, D. A., Carswell, E. A., and Stockert, E. (1961). *Cancer Research*, **21**, 1281.
Old, L. J., and Boyse, E. A. (1964). *Annual Review of Medicine*, **15**,167.
Reiner, J., and Southam, C. M. (1966). *Nature*, **210**, 429.
Rosenau, W., and Moon, H. D. (1967). *Cancer Research*, **27**, 1973.
Sokoloff, B., *et al.* (1961). *Growth*, **25**, 249.
Thunold, S. (1967). *Acta Pathologica et Microbiologica Scandinavica*, **69**, 521.
Treadwell, A. de G., Gardener, W. U., and Lawrence, J. H. (1943). *Endocrinology*, **32**, 161.
Weiss, D. W., Bonhag, R. S., and DeOme, K. B. (1961). *Nature*, **190**, 889.
Woodruff, M. F. A., and Boak, J. L. (1966). *British Journal of Cancer*, **20**, 345.
Yamaguchi, I., Takahashi, T., Narisawa, T., and Hiroki, T. (1965). *Tohoku Journal of Experimental Medicine*, **87**, 338.

Evaluation of Silicone as an Artificial Lubricant in Osteoarthrotic Joints

V. WRIGHT, D. I. HASLOCK, D. DOWSON, P. C. SELLER, B. REEVES

British Medical Journal, 1971, **2**, 370–373

Summary

Silicone 300 has been evaluated as an artificial lubricant in osteoarthrotic joints by means of a pilot study in five inpatients and a control trial of 25 outpatients with 40 osteoarthrotic knees. Sequential analysis showed a significant benefit from saline compared with silicone at one week follow-up and no significant difference at one month.

Measurement of stiffness with a knee arthrograph showed no difference in reduction of stiffness between the two substances. In a study of 18 rabbits there was no evidence that silicone was retained in the joint cavity for longer than 48 hours. There was a failure of clearance of iodinated serum albumin for as long as three to four days after the injection of silicone, suggesting some obstruction to lymphatic outflow. Experimentally produced cartilaginous defects did not heal quicker with the injection of silicone into the joint.

Bio-engineering Group for the Study of Human Joints, University of Leeds, Leeds LS2 9PJ

V. WRIGHT, M.D., F.R.C.P., Professor of Rheumatology
D. I. HASLOCK, M.B., CH.B., Registrar in Rheumatology
D. DOWSON, PH.D., F.I.MECH.E., Professor of Engineering, Fluid Mechanics, and Tribology
P. C. SELLER, M.SC., Research Student

Leeds Regional Hospital Board

B. REEVES, M.S., F.R.C.S., Consultant Orthopaedic Surgeon

Introduction

The nature of the lubrication process in human joints has undergone extensive studies in recent years. A number of workers have investigated the normal lubricating mechanism (McCutchen, 1959; Charnley, 1960; Barnett and Cobbold, 1962; Dintenfass, 1963; Tanner, 1966; Maroudas, 1967; Dowson *et al.*, 1968), the way in which it fails in pathological conditions, and the possibility of producing an artificial lubricant for therapeutic use (Helal and Karadi, 1968; Nuki *et al.*, 1969; Seller *et al.*, 1969). We have previously suggested the following criteria for an artificial lubricant. It should behave in friction tests and on scanning electron microscopy like hyaluronic acid-protein complex. It should resist thermal, mechanical, and oxidative degradation. It should be tolerable within the joint space and be retained there. It should be cheap and easy to produce. However, other workers have reported the successful use of a silicone fluid in osteoarthrosis (Helal and Karadi, 1968). To evaluate silicone 300* as an artificial lubricant a pilot study was conducted and a controlled trial was performed.

Patients and Methods

A pilot study of five inpatients with osteoarthrosis demonstrated clinically and radiologically in one or more knees was undertaken. The more severely affected knee in each patient was injected with silicone, the patients being assessed before injection and daily for one week thereafter. Long-term follow-up was continued in the outpatient department. The amount of pain was recorded on a rating scale (0 = none, 1 = mild,

* Silicone of nominal viscosity 300 centistokes, grade F111, was supplied by I.C.I.