social theorists, were left to be caught up in the net of the growing enthusiasm for the picturesque, the romantic, and the vaguely religious quest for the Noble Savage in antiquity.

Against this background Stukeley's personal history becomes more explicable. There certainly seems to have been an intellectual and emotional crisis in his life about 1729, and one is reminded of Newton's nervous crisis of 1692-3. We saw how the two men discussed Biblical antiquities together, and in 1731 Stukeley drafted a *Mosaic Chronology* on a topic dear to Newton's heart. He was becoming concerned with a framework of the ancient world within which he could set his prehistoric monuments; he needed an "explanation" within the terms of which Avebury, Stonehenge, and the rest would make some sort of sense beyond the limits of description, order, and classification. That "explanation" had in fact constituted something new and acceptable in the Royal Society's approach a century before, but it no longer satisfied contemporary demands of intellect and emotion, and it no longer satisfied Stukeley.

Unfinished Manuscripts

Among his manuscripts are several drafts of the book he never finished. As early as 1723 it was planned as *The History of the Temples of the Ancient Celts*, but, ten years later, four years after he had retired from medicine and taken Holy Orders, this had become emended to *The History of the Religion and Temples of the Druids*. Nevertheless, in 1740 a book on Stonehenge and three years later a companion volume of Avebury were published, announced by Stukeley to be two sections only of a seven-volume treatise on patriarchal Christianity, of which no more appeared. Had they done so the remaining five would have been introductory, beginning with ancient chronology and going on to demonstrate that "the first religion was no other than Christianity . . . that all mankind from the Creation had a knowledge of the plurality of persons in the Deity" and that

Phoenicians had colonized Britain, bringing patriarchal religion with them "about the time of Abraham" in the persons of the Druids, who were "of Abraham's religion intirely" and though "we cannot say that Jehovah appeared personally to them they had the notion and expectation of the Messiah."

Such a demonstration would, Stukeley thought, "combat the Deists from an unexpected quarter"—so unexpected indeed that no one seems to have recognized his books as contributions to contemporary religious controversy at all. But Stukeley was quite logical. On the one hand, this dispute involved churchmen like himself to whom divine revelation, the coming of the Messiah and the fulfilment of prophecy, and the doctrine of the Trinity, were among the foundations of their faith. On the other hand, the Deists, confident of the original nobility and perfectibility of a man from the Creation, and convinced by the mathematicians of a divinely ordered universe, found that "The State of Nature was the reign of God," as Pope put it, and that revelation and the miraculous elements in Christianity were irrelevant. One way to attack this disturbing view was to make "Christianity as Old as the Creation" as part of the title of Tindal's book of 1730 puts it, and Stukeley—by now so devoted to his ancient Druids that he must have thought of them as prehistoric fellow clergymen—followed Tindal and others who were confounding Deism by making Christianity the original religion of nature.

Noble Druids, natural Christians, stout patriots in the face of Roman rule, and worshipping at Stonehenge—all this was immediately acceptable to men of feeling and sensibility as well as to gentlemen of taste in the mid-eighteenth century. As the momentum of the Romantic Movement increased (and Macpherson's Ossian fabrications had their first wild success around the time of Stukeley's death), so these ideas became more deeply embedded in our national folklore, and we are by now a very long way from the scientific curiosity which prompted Stukeley's painstaking records and measurements of two great prehistoric monuments in the 1720s.

Occasional Survey

Treatment of Paget's Disease of Bone with Synthetic Salmon Calcitonin

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Summary

Thirteen patients with painful Paget's disease of bone were treated as outpatients with low doses of synthetic salmon calcitonin 22.5-50 µg three times weekly. Treatment produced full remission of pain in a mean time of 5.5 weeks and

a mean depression of serum alkaline phosphatase activity of 33%.

The interval before symptomatic relief could not be predicted from the variables studied. The ultimate fall in serum alkaline phosphatase activity, however, could be predicted from the initial levels and from the early rate of decrease ($P < 0.001$). Biochemical resistance to treatment, which occurred in three cases, could be related to the dose and duration of treatment.

Prolonged remissions of pain may occur which are not related to biochemical remission, to the dose of calcitonin, or to the duration of treatment. The side effects attributable to salmon calcitonin were transient nausea (in nine patients), transient flushing (in four), diarrhoea (in two), and rash (in one) though in only one patient did treatment have to be withdrawn prematurely because of these effects.

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Introduction

Paget's disease of bone is common and its aetiology is unknown. Most patients with the disorder have no symptoms, but in a minority pain may be severe, deformity may develop, the affected bones are predisposed to fracture, nerve compression, may occur, and osteogenic sarcoma may be a terminal complication. The disease resembles in its behaviour a benign tumour of bone because of the characteristic largely autonomous and disorganized bone resorption and formation.¹

Many methods of treatment, mostly empirical, have been proposed. These include the use of aspirin,² adrenocorticotrophin and cortisone,³ and sodium fluoride.⁴ A biochemical response has been shown after the use of more specific agents such as mithramycin,⁵ actinomycin D,⁶ diphosphonates,⁷ calcitonin,⁸ and glucagon, which stimulates the release of endogenous calcitonin.⁹

After treatment with calcitonin pain remits and the rate of resorption of bone is reduced. At the same time the new bone formed may be normal in structure.⁸ Both human and porcine calcitonin are given by injection twice or thrice daily.^{8,10} Salmon calcitonin, which is much more potent and acts longer,¹¹ has not been used as widely as either human or porcine calcitonin.

We used salmon calcitonin in a regimen of thrice weekly injections in cases of Paget's disease where this was justified on the grounds of pain, and our results are described here.

Patients and Methods

Thirteen patients (table I) were studied during 15 courses of treatment. Selection for treatment was based primarily on a complaint of pain attributed to Paget's disease, supported by radiographical evidence. The presence of throbbing pain both at night and at rest was noted by each of these patients.

Some of the earlier patients studied were admitted to the metabolic unit for a short period of balance study to investigate the acute effects of salmon and porcine calcitonin. The results of these studies are reported elsewhere.¹² These patients and others not so fully investigated were treated and reviewed weekly as outpatients.

Synthetic salmon calcitonin 45 µg/ml in saline at pH 4.2 was given in a dose of 22.5-50 µg (equivalent to 68-150 M.R.C. units) by intramuscular injection three times a week. Periods of treatment extended up to nine months. At each weekly attendance serum alkaline phosphatase (S.A.P.) activ-

ity, serum calcium, and plasma phosphate concentrations were determined. After a course of treatment patients were reviewed less often and a further course was given if pain recurred.

S.A.P. was estimated by a modification of the method of Kind and King,¹³ and results are expressed in IU/l. The coefficient of variation of this method is 1.80% at a level of 100 IU/l.

Results

Further details of the patients and their treatment are given in table II. Additional data on some patients are given below.

CASE REPORTS

Case 1.—The clinical response to treatment was incomplete. Though throbbing pain at rest was abolished residual pain in the lumbar region could be ascribed to coincident osteoporosis.

Case 2.—A course of porcine calcitonin had been given seven months previously with remission of pain in the right leg. Treatment with salmon calcitonin was started when this symptom recurred. Rapid remission of pain and of local heat occurred within three weeks. During the last week of treatment the patient complained once more of pain in the leg though S.A.P. activity remained depressed. Radiographs showed the development of osteogenic sarcoma, to which he succumbed despite radical surgery, radiotherapy, and further injections of salmon calcitonin.

Case 3.—Two previous courses of treatment with porcine calcitonin had been given at intervals of one year with full relief of pain. Treatment with salmon calcitonin was stopped after five weeks because the patient developed a rash, but by this time pain had disappeared.

Case 4.—Relief of headache and lumbar pain occurred in this patient. Residual pain in a knee and hip was attributed to rheumatoid arthritis and osteoarthritis.

Case 5.—A course of porcine calcitonin had been given one year previously with full relief of pain. Treatment with salmon calcitonin was abandoned after three weeks because of the severity of side effects.

Case 6.—Two previous courses of treatment with porcine calcitonin resulted in complete relief of symptoms for nine and 18 months. Full remission for 14 months resulted from treatment with salmon calcitonin. The patient was then given an additional course of salmon calcitonin with similar results. She gave her own injections.

Case 7.—A second course of salmon calcitonin was given after an interval of four months because of recurrence of pain.

TABLE I—Initial Serum Alkaline Phosphatase Levels, Extent of Radiographical Abnormalities, and Symptoms of 13 Patients

Case No.	Treatment No.	Mean S.A.P. IU/l. Before Treatment	Extent of Radiographical Changes	Other Radiographical Abnormalities	Site of Pain	Duration of Pain
1	1	225	3rd lumbar vertebra; sacrum; L. hemipelvis	Osteoporosis	Lumbar	2 Years
2	2	374	L. humerus; L. hemipelvis; L. femur; R. tibia and fibula		R. leg	10 Years
3	3	304	L. hemipelvis; tibia; fibula; os calcis	Osteoarthritis	L. leg	8 Years
4	4	304	Skull; lumbar spine; hands; 4th cervical vertebra	Rheumatoid changes of hands and hips	Head; knees; hips lumbar region	3 Years
5	5	175	L. hemipelvis; sacrum; R. tibia and fibula	-	R. knee	4 Months
6	6	87	R. tibia	-	R. leg	2 Years
7	7	109	R. tibia	-	R. leg	1 Month
8	8	252	R. hemipelvis; R. tibia	-	R. leg	10 Years
9	9	236	R. hemipelvis; R. tibia	-	R. leg	1 Month
10	10	296	1st and 2nd lumbar vertebrae; L. hemipelvis	-	L. hip; L. leg	2 Years
11	11	128	2nd and 4th lumbar vertebrae; L. hemipelvis and femur	-	L. hip	3 Months
12	12	261	Skull; pelvis; L. femur and tibia; R. tibia	-	L. thigh	12 Years
13	13	97	Sacrum; L. innominate bone and femur	-	Lumbar region; L. leg	6 Years
14	14	570	3rd cervical vertebra; all lumbar vertebrae; skull; pelvis	-	Both thighs	6 Months
15	15	1,265	Skull; lumbar spine; pelvis; L. humerus, ulna, and os calcis; R. radius, ulna, and femur	-	Lumbar region; L. knee and heel	4 Years 2 Years

TABLE II—Clinical Details of 13 Patients Treated with Calcitonin including Degree of Symptomatic Relief

Case No.	Sex	Treatment No.	Age (Years)	Individual Dose of Salmon Calcitonin* (µg)	Duration of Treatment (Weeks)	Total Dose of Salmon Calcitonin (µg)	Degree of Symptomatic Relief§	Interval Before Relief of Symptoms (Weeks)	% Fall of S.A.P.	Rate of Fall of S.A.P. IU/l./week
1	M.	1	81	45	14	1,890	+	11	33	5
2	M.	2	59	45	14	1,890	++	3	54	22
3	F.	3	70	50	5	755	++	3	19	10
4	F.	4	60	45	35	4,705‡	++	6	41	6
5	M.	5	65	22.5	3	219	—	—	0	4
6	F.	6	69	25	10	730	++	3	9	1
7	F.	7	70	50	6	900	++	3	21	4
8	F.	8	78	45	14	1,890	++	11	38	6
9	F.	9	78	40	25	3,000	++	12	47	7
10	M.	10	60	45	30†	2,250‡	++	13	51	17
11	F.	11	67	45	15	2,095	++	3	36	3
12	M.	12	67	22.5	7	511	—	—	4	2
13	M.	13	59	45	6	810	++	6	25	3
12	F.	14	75	45	32	4,320‡	++	5	62	39
13	M.	15	53	45	6	810	++	3	56	118

*Individual doses shown varied slightly with different batches of ampoules used in course of a period of treatment.

†Duration of treatment was 10 weeks with thrice weekly injections and then 20 further weeks with weekly injections.

‡Treatment was associated with onset of biochemical resistance during period of treatment.

§ ++ = Full remission. + = Partial response. — = No change of symptoms.

Case 10.—This was the only patient we found whose pain and S.A.P. activity did not respond to treatment over a period of seven weeks.

CLINICAL FEATURES

Relief of bone pain occurred in all patients except two. In one (case 5) treatment was discontinued prematurely, and it is possible that the smaller dose given to the other patient (case 10) was inadequate. Relief of symptoms in the remaining patients occurred after three to 11 weeks (mean 5.5 weeks). In those two patients who were treated twice the time interval needed to achieve relief of pain was identical even though one of them (case 6) had received twice the dose of salmon calcitonin in her second course of treatment. In two patients (cases 2 and 7) the skin temperature of the affected leg fell after treatment.

The time taken to achieve remission of pain during treatment did not correlate with the initial S.A.P. activity, the rate of fall, or the percentage fall of S.A.P. values or with the duration of symptoms before treatment. Thus the length of treatment needed for relief of pain could not be predicted from these variables.

Freedom from pain invariably persisted after treatment, even when S.A.P. activity remained increased at the end of treatment. The shortest period of remission of pain after treatment was four months (case 7, treatment 8) and the longest was continuing 17 months after treatment (case 9).

BIOCHEMICAL RESULTS

Salmon calcitonin given thrice weekly had no long-term effect on serum calcium and plasma phosphate concentrations, which did not change significantly during the course of treatment. Striking changes, however, were seen in the S.A.P. activity, which was measured serially (fig. 1). S.A.P. activity decreased during the early phase of treatment and this was clearly evident after six weeks. The initial fall was roughly linear with time, and the rate of fall of mean S.A.P. activities was calculated from this early phase. The percentage fall of S.A.P. activity was estimated for each patient from the initial S.A.P. value and the lowest mean S.A.P. value during treatment (see table II). The mean S.A.P. activity before treatment for all the patients was 312 (S.E. 75) IU/l. This subsequently fell at a mean rate of 17 (S.E. 8) IU/l./week to a nadir of 67% (S.E. 5) of the initial reading. If the patient (case 5) whose treatment was prematurely withdrawn and the patient (case 10) who did not respond are omitted from the calculations the rate of fall and percentage fall increase to 19 (S.E. 9) IU/l./week and 62% (S.E. 5) respectively.

The behaviour of the S.A.P. activity in response to treat-

FIG. 1—Serial determinations of serum alkaline phosphatase (S.A.P.) activity in 13 patients during 15 courses of treatment with salmon calcitonin for pain in Paget's disease. All points shown are means of at least three determinations. ● = values during treatment. × = values after withdrawal of treatment. Numbers on left refer to patients, and those on right refer to treatment number.

ment is related to the height of the initial value (fig. 2). The degree of suppression of S.A.P. activity may be estimated best from the initial S.A.P. values (fig. 2 (c)). The S.A.P. levels of only the three patients (cases 6, 9, and 11) with initial S.A.P. activities of 128 or less suppressed to within the normal range (20–85 IU/l.).

Serial determinations of S.A.P. indicated the time sequence of biochemical events (fig. 3; P values are based on paired *t* tests). The rate of fall of S.A.P. activity was greatest up to nine weeks of treatment and then diminished progressively until the 21st week. In cases where treatment was continued thereafter S.A.P. values began to rise. Such a response is shown in fig. 4 for one patient (case 4) who was given salmon calcitonin for 35 weeks to a total cumulative dose of 4,705 µg. Remission of symptoms occurred well before maximum depression of S.A.P. activity, and tolerance seemed to occur at the 22nd week, after the administration of 3,000 µg. After withdrawal of salmon calcitonin the S.A.P. activity continued to rise. Two other patients (cases 8 and 12) also developed evidence of resistance. They had received, respectively, 2,200

FIG. 2—Correlations of serum alkaline phosphatase (S.A.P.) activity throughout study.

FIG. 3—Incremental percentage changes in serial mean serum alkaline phosphatase (S.A.P.) activities (mean of periods of 3 weeks $\pm$ S.E.) during treatment and after withdrawal of treatment. First mean reading after treatment is derived from comparison with mean of last readings obtained during treatment (see text).

FIG. 4—Serial mean serum alkaline phosphatase (S.A.P.) activities in case 4 showing onset of biochemical resistance during treatment.

and 3,600 μ g of salmon calcitonin for periods of 27 weeks when tolerance became evident.

After withdrawal of treatment (fig. 3) the mean S.A.P. activity rose by 4% within the first three weeks and thereafter rose incrementally by about 10% of the previous reading per period till pretreatment levels had been reached.

Case 8 (fig. 5) received 45 μ g salmon calcitonin three times a week for 10 weeks, and while this treatment was accompanied by a fall of S.A.P. activity, his symptoms failed to remit. Further treatment with salmon calcitonin 45 μ g once weekly only, however, resulted in a continuing decline in S.A.P. activity and disappearance of pain by the 13th week of treatment. Thus, on the evidence of this patient a clinical and biochemical response can follow treatment given at weekly intervals. Since S.A.P. activities invariably rose in all our patients within nine weeks of withdrawal of salmon calcitonin, the response to weekly injections in this patient can be regarded as authentic.

FIG. 5—Serial mean serum alkaline phosphatase (S.A.P.) activities in case 8 showing effect of salmon calcitonin thrice weekly followed by weekly injections.

SIDE EFFECTS

Nine patients complained of nausea, four of transient flushing, and two of diarrhoea. Nausea occurred only at the beginning of treatment and was effectively controlled in all save one patient (case 5) by cyclizine or metoclopramide given by mouth 30 minutes before the injection; the need for this was overcome within two weeks in the other eight patients. Where possible patients received their injections before going to bed so that the sedative effect of the antiemetic did not inconvenience them. Transient flushes were not disturbing. Diarrhoea occurred in two patients. In case 2 the patient had two or three watery motions after each injection. In case 5 diarrhoea and nausea were so incapacitating that treatment was withdrawn after three weeks. One patient (case 3) developed a maculopapular rash after five weeks of treatment. At that time the rash could not be specifically ascribed to salmon calcitonin, but as remission from pain had occurred it was thought prudent to discontinue treatment. A later course of treatment, however, resulted in a similar sequence of events.

In most patients side effects were either easily controlled or were not an inconvenience. Biochemical evidence of drug toxicity was not found in these patients; details of the screening undertaken will be reported elsewhere.¹²

Discussion

We fully recognize the fallacies that can attach to the relief of subjective evidence of disease. Nevertheless, the striking

features in our patients were the delay in onset of relief of pain associated with Paget's disease and the consistency of the relief, which persisted after treatment with salmon calcitonin had ended. This type of response is not seen with certain other forms of treatment—for example, fluorides⁴ or diphosphonates.⁷ The reduction in S.A.P. activity and other metabolic responses observed¹² together with the recurrence of pain after considerable intervals without treatment further support the view that salmon calcitonin is effective in the management of Paget's disease.

The most prominent side effect of salmon calcitonin was nausea, which was controlled in all except one patient by the routine use of oral antiemetics. Like the patient studied by Schuhmacher *et al.*¹⁴ our patients rapidly came to tolerate the injection of salmon calcitonin without a continuing need for antiemetics.

Both human and porcine calcitonin have been used effectively in small series of patients with bone pain.^{8, 10, 15} These preparations are usually given twice or thrice daily and previous reports on the use of salmon calcitonin describe regimens of daily injections.^{14, 16} Because salmon calcitonin has a greater duration of action compared with other preparations we assessed the value of less frequent administration. Our thrice weekly regimen can suppress pain and lower raised S.A.P. activity, and, furthermore, the relief of pain can be maintained for periods as long as 17 months after the end of treatment.

We did not measure the incidence of antibodies to salmon calcitonin. Antibody formation occurs after treatment with porcine and salmon calcitonin in about half of patients treated for over four months.¹⁷ It occurs more often after porcine calcitonin than after salmon calcitonin but seldom gives rise to clinical or biochemical resistance. Antibody formation has not yet been reported after treatment with human calcitonin though presumably it could occur in much the same way as after the administration of human growth hormone. Three of our patients developed biochemical evidence of tolerance. This became evident after the patients had received more than 3,000 μg (mean 3,758 S.E. 762) over periods of 22 weeks or longer.

The dose of salmon calcitonin used by us ranged from 22.5 to 50 μg —that is, a maximum weekly dose of 150 μg . This was considerably lower than in some series of patients where doses of 230 μg ¹⁴ or even 4,100 μg ¹⁷ per week were used. Goldfield *et al.*¹⁶ treated three patients by daily injections for 90 days in doses similar to those used by us, with symptomatic relief in two. The optimum dose of salmon calcitonin therefore remains undecided. Our studies show that symptomatic relief may occur within three weeks and almost invariably by the 13th week of treatment. Furthermore, treatment with as little as 730 μg over 10 weeks may result in a prolonged remission from pain—for example, case 6.

Our results permit the following generalizations on this treatment.

Firstly, the expected degree of suppression of S.A.P. activity can be predicted from the initial S.A.P. value as well as from its rate of fall over the first six weeks (fig. 2 (c) and (d)). Once this low value has been reached, it seems prudent to minimize the risk of antigenic stimulation and to withdraw treatment provided symptomatic relief has occurred.

Secondly, the maximal rate of suppression of S.A.P. activity occurs at the ninth week of treatment (fig. 3) and symptomatic relief is complete on average by the sixth week (table II). If our patients were representative of those with Paget's disease as a whole remission of symptoms should occur within 13.5 weeks (95% confidence limits). We suggest that treatment should be withdrawn if remission has not occurred by this time.

Thirdly, the dose of salmon calcitonin used by us ranged from 67.5 μg to 150 μg weekly and was adequate in most patients. It is not yet clear, however, whether as small a dose as 22.5 μg thrice weekly is sufficient. Certainly one

patient (case 10) gave no response to this dose after seven weeks whereas case 8 (fig. 5) continued his clinical and biochemical response with an even smaller dose—namely, 45 μg weekly. As little as 0.2 μg of salmon calcitonin intravenously has an effect on hydroxyproline excretion.¹⁸ Much smaller doses than we have used might therefore be equally effective.

The ease with which salmon calcitonin can be used and its low toxicity makes it reasonable to treat patients with Paget's disease as outpatients. One of our patients learned to inject herself while others depended upon the district nurse or local hospitals. With increasing experience patients could ultimately be treated and monitored by their own general practitioner.

The desirability of treating most patients with symptomless Paget's disease is questionable. On the other hand the pain of Paget's disease amply justifies the treatment described. In addition, treatment with calcitonin has been reported to result in normal new bone formation,⁸ radiographical improvement,^{19, 20} and the improvement of entrapment neuropathy.¹⁵ It remains to be confirmed that treatment can prevent fractures, progressive deformity, or other complications. Among these complications osteogenic sarcoma is often rapidly fatal and is unresponsive to conventional therapy. Since some features of Paget's disease can be shown to respond to treatment with calcitonin and, though the hormone may not affect an established sarcoma,²¹ it might possibly reduce the incidence or delay the onset of this important complication²² in, for example, a patient such as case 2. Thus treatment with calcitonin may be justified in an increasing proportion of patients with Paget's disease. Because of the risks of antigenic stimulation with prolonged usage of salmon (and porcine) calcitonin, however, we recommend short courses of treatment using a low dose. The case for long-term "suppressive" treatment with salmon or porcine calcitonin remains to be made and will require systematic clinical investigation.

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