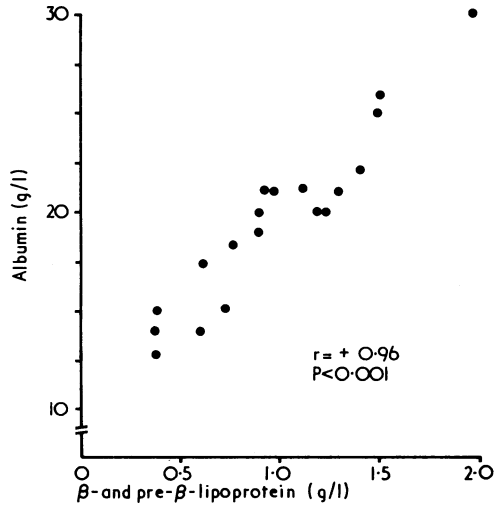
served as controls. Serum lipids, albumin, and total proteins were determined by standard techniques. Serum β- and pre-β-lipoproteins were measured turbidimetrically.[2]

Serum concentrations of cholesterol, triglyceride, and β- and pre-β-lipoproteins were appreciably lower in the kwashiorkor children than in the control children ($P<0.001$ in all instances). The fig. shows a direct proportion between the concentrations of serum albumin and serum β- and pre-β-lipoproteins in kwashiorkor children.



Relationship between serum albumin concentrations and serum β- and pre-β-lipoprotein concentrations in children with kwashiorkor.

Discussion

We have shown by a simple quantitative technique using the selective precipitation of β- and pre-β-lipoproteins that the serum concentrations of these lipoproteins were decreased in children with kwashiorkor. The concentrations of serum cholesterol and triglyceride were also decreased. Since cholesterol and triglyceride are the major transport cargo of β- and pre-β-lipoproteins, the accumulation of fat in the liver of children with kwashiorkor may be partly due to the impaired release of these lipids from the liver into the plasma.[1] In addition the concentrations of serum albumin are directly proportional to the concentrations of serum β- and pre-β-lipoproteins in children with kwashiorkor. This is not the case in the fatty liver induced in rats by feeding orotic acid, an inhibitor of protein synthesis. Experimentally, though a total inhibition of the synthesis of β-lipoproteins occurs, the synthesis of albumin remains unchanged. An impaired synthesis of albumin in kwashiorkor, however, has been noted.[4] We suggest that a diminished synthesis of β- and pre-β-lipoproteins may accompany the diminished synthesis of albumin. Thus the impairment of the synthesis and possibly the transport functions of these proteins may result in a generalized poor nutritional state of the cells and tissues. This may render kwashiorkor children more susceptible to infections[5] and probably account for their striking cerebral lethargy.

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Oral Contraceptives and Myocardial Infarction in Young Women: A Further Report

We have recently reported an increased risk of myocardial infarction among women using oral contraceptives.[1] The conclusions were based on a controlled investigation of 58 women under 45 years of age who had survived myocardial infarction during 1968-72 in two hospital regions of England and Wales. The nature of the findings was such that it was thought desirable to submit them for publication before the collection of data in a third region was complete. The results for a similar group of patients investigated in the Wessex Region are presented in this report.

Patients, Methods, and Results

The methods for the selection of myocardial infarction and control patients and the investigation procedure in the North-West Metropolitan and Oxford Regions were described in detail in our previous publication. In the Wessex Region myocardial infarction patients and controls (three patients matched with each infarction patient in respect of marital status, five-year age group, and year of hospital admission) were identified by the medical information unit of the regional health authority. Altogether 21 myocardial infarction patients (aged 32 to 44 years) were identified in the Wessex Region, but four had died in hospital or before the study was undertaken and three could not be traced. The diagnoses of the control patients, methods of data collection, and statistical analyses were similar to those reported.[1]

The oral contraceptive practice of the Wessex patients and of the consolidated group of 72 infarction patients and their controls is shown in the table.

Oral Contraceptive Practice Among Patients with Myocardial Infarction (M.I.) and Controls

Oral Contraceptive Practice	Wessex Patients		Consolidated Patients	
	No. (%) of Patients with M.I.	No. (%) of Controls	No. (%) of Patients with M.I.	No. (%) of Controls
Never used	9 (64·3)	18 (75·0)	44 (61·1)	150 (78·9)
Used during month before admission	3 (21·4)	2 (8·3)	20 (27·8)	16 (8·4)*
Used only more than one month before admission	2 (14·3)	4 (16·7)	8 (11·1)	24 (12·6)
Total	14 (100·0)	24 (100·0)	72 (100·0)	190 (100·0)

*Comparison between proportions of patients using oral contraceptives during the month before admission: $\chi^2 = 13{\cdot}28$, $P<0.001$.

For the consolidated group the proportion of patients who had used oral contraceptives during the month before admission was significantly higher amongst the patients with infarction than among the controls ($P<0.001$), as was the proportion of those who had used oral contraceptives at any time ($P<0.01$). No appreciable difference was, however, apparent in the proportions who had used oral contraceptives only at some time in the past. The risk of admission for myocardial infarction in women who had been using oral contraceptives in the previous month relative to that in women who were not currently using them is estimated from these figures to be 4·2 to 1. After standardization for possible confounding by other risk factors for myocardial infarction (hypertension, pre-eclamptic toxaemia, cigarette smoking, and hypercholesterolaemia) the risk ratio was 3·1 to 1. This threefold increase in risk attributable to oral contraceptives was significant at the 2% level.

Comment

The difference in oral contraceptive use between the two groups of patients in the Wessex region is very similar to that which might have been expected from the experience in the larger group of subjects but does not reach statistical significance when examined independently. This is hardly surprising because the numbers are so small. The findings are, however, considered to be of particular interest since the method of ascertainment used should have identified all cases of non-fatal myocardial infarction in this region and provide confirmatory evidence of the association between oral contraceptive use and myocardial infarction in young women.

We are grateful to Professor M. Alderson for his help with patient identification and for obtaining permission from the appropriate consultants;

Professor M. P. Vessey and Sir Richard Doll gave helpful advice and encouragement.

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Treatment of Paget's Disease of Bone with once a week Injections of Salmon Calcitonin

Human, porcine, and salmon calcitonins are effective in treating Paget's disease in doses of 1-8 M.R.C. units/kg body weight daily or three times weekly.[1] [2] We have used 50 M.R.C. units of salmon calcitonin (S.C.T.) three times weekly as the minimal practical dose for long-term treatment of symptomatic generalized disease,[2] but the similarity of clinical and biochemical results on 100 units/day prompted us to explore the effectiveness of smaller doses given less often in patients with limited symptomatic disease.

Patients, Methods, and Results

Nine patients were treated with S.C.T. 50 units/week by self-injection for 10-16 months. Three patients had generalized and six limited lesions of Paget's disease (see table). All had pain in afflicted areas and none had neurological complications. Before S.C.T. treatment each patient had physical, neurological, slit lamp, audiometric, and complete skeletal examinations and an electrocardiogram. Fasting blood for serum calcium, phosphorus, magnesium, alkaline phosphatase, and creatinine and a 24-hour urine collection for calcium, phosphorus, total hydroxyproline, and creatinine were obtained each week for three weeks before treatment and were repeated at six to eight-week intervals.[2] Our patients had partial restrictions on foods containing hydroxyproline. All biochemical determinations were performed in duplicate; the reproducibility of the hydroxyproline determination was 5%. Plasma was tested for binding antibodies to S.C.T.[2]

Before treatment serum alkaline phosphatase was raised in eight patients (mean 76 K.A. units). Mean minimal and final values during treatment were 39 and 51 K.A. units respectively. The decrease in serum alkaline phosphatase averaged 28%. Urinary hydroxyproline was initially raised in all patients (mean 1·30 mmol/24 h (170 mg/24 h)). Urinary hydroxyproline decreased in six patients during S.C.T. treatment (mean decrease after eight months' treatment 28%, and after 16 months 18%). Three patients (cases 3, 5, and 7) showed no significant trend in hydroxyproline values during treatment. Binding antibody studies after 7-16 months gave uniformly negative results. The hypocalcaemic effect of 50 units of S.C.T. was tested in five patients at the end of treatment. Serum calcium decreased by 0·25-0·65 mmol/l (1·0-2·6 mg/100 ml) during one to eight hours in all five patients. S.C.T. was well tolerated except in four patients who experienced mild nausea after injections, which did not necessitate withdrawal of S.C.T. On treatment pain disappeared or decreased appreciably in cases 1, 3, 4, 6, 7, and 8; decreased slightly in case 9; and was unchanged in cases 2 and 5. Improvement often started within four weeks, but maximum benefit was not achieved until after three to four months of treatment. In the two patients (cases 1 and 6) with increased skin temperature, tested by palpation of afflicted legs, the temperature decreased significantly during treatment.

Discussion

Serum alkaline phosphatase and urinary hydroxyproline levels and bone pain, deformities, and neurological complications indicate the activity of Paget's disease. S.C.T. 50 units/week decreased the biochemical values in most patients, and this was not a placebo effect.[3] Seven cases of pain relief was beyond the expected 30% spontaneous improvement rate reported with placebos.[4] After a mean of 19 months' treatment with S.C.T. 50-100 units three times weekly mean serum alkaline phosphatase and urinary hydroxyproline decreased by 48% and 52% respectively.[2] Corresponding mean changes for our patients treated with 50 units/week were, as expected, smaller—28% and 18%. Three patients' failure to decrease total hydroxyproline may have been a further example of dissociation in the responses of individual values which is not due to antibody formation.[2] S.C.T.'s continued biological effectiveness was attested to by its ability to induce significant hypocalcaemia. Over half our patients improved on this low dose without incurring S.C.T. antibody formation, which supports the suggestion that hormones in small doses given infrequently may influence bone metabolism. Possibly, weekly injections of S.C.T. might maintain therapeutic benefits achieved by more vigorous treatments such as daily S.C.T., mithramycin,[5] or diphosphonates.[4]

We are indebted to the staffs of the U.S.P.H.S. Clinical Research Center and the Bone Clinic of State University Hospital and to Drs. James Lesh and William Parsons of the Armour Pharmaceutical Company for supplying S.C.T.

This study was supported by Grant RR-318 from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health and a grant from the Armour Pharmaceutical Company.

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Clinical and Biochemical Characteristics of Nine Patients with Paget's disease

Case No.	Age and Sex	Clinical Features						Biochemical Features	
		Duration of Disease (Years)	Extent of Disease*	Bone Pain	Deformity and/or Increased Head Size	Impaired Hearing	Increased Temperature over Afflicted Area	Serum Alkaline† Phosphatase (K.A. Units)	Urinary Total Hydroxyproline‡ (mmol/24 h)
1	68 F.	15	Sk., S., L., P.	+	+	−	+	186	2·82
2	64 M.	6	S., L., P.	+	−	−	−	69	1·65
3	66 F.	20	S., L., P.	+	−	−	−	38	0·97
4	78 M.	25	S., P.	+	−	+	−	61	0·98
5	54 F.	6	S., P.	+	−	−	−	25	0·76
6	49 F.	5	L.	+	+	−	+	41	0·85
7	70 F.	10	Sk.	+	+	+	−	166	2·46
8	62 M.	2	P.	+	−	−	−	20	0·65
9	55 M.	5	L.	+	−	−	−	7	0·52

*Sk. = Skull. S. = Spine. L. = Long bones. P. = Pelvis.
†Normal <14 K.A. Units
‡*Conversion: SI to Traditional Units*—1 mmol/24 h ≈ 131 mg/24 h. Normal <0·34 mmol/24 h on hydroxyproline-free diet.