not explain the trend. We can only speculate on factors such as subclinical infections, or length of daylight.

Summary

We report an analysis of 3,243 cases of squint examined at a health department clinic and an eye hospital. The estimated prevalence of squint at the age of 6 years is 4.3%, similar to estimates in other surveys in England. Incidence of onset is highest in the third year of life, and, if this distribution reflects the incidence in the community, it represents one characteristic pattern of distribution. Another pattern has been described in which the highest rate of onset is in the first year and diminishes rapidly thereafter. Non-central viewing occurs in 23% of the cases of squint in which this function could be assessed. Non-central viewing is much more frequent in boys, in children in whom the onset is early, in those who have had the squint for a longer period, and in those with high degrees of anisometropia. There is evidence that squints begin more often in winter, with a peak incidence in January.

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Progestin Therapy of Breast Cancer: Comparison of Agents

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Over recent years many synthetic orally active progestational agents have been introduced to clinical practice. The multiplicity of such agents presents a problem of choice to the clinician considering progestin therapy in breast cancer. A similar problem applies also to uterine cancer. Various authors, each using a different progestin, have reported their results in small series of breast cancer cases (Jonsson *et al.*, 1959 ; Lewin *et al.*, 1959 ; Douglas *et al.*, 1960 ; Baker and Kelley, 1960 ; Jolles, 1962 ; Bucalossi *et al.*, 1963 ; Stoll, 1965). The trials are summarized in Table I, and from the results it is obvious that there is a place for progestin therapy in breast cancer. To our knowledge no basis has yet been shown for statements that the presence of breast cancer contraindicates the use of progestins because they may possibly stimulate the tumour (Klawans, 1965).

TABLE I.—*Reports of Clinical Response in Breast Cancer After Progestin Administration*

Author	Progestin	Clinical Response in
Jonsson *et al.* (1959) ..	Bromoketoprogesterone	7 of 34
Lewin *et al.* (1959) ..	Norethindrone	5 „ 22
Douglas *et al.* (1960) ..	Norethisterone oenanthate	1 „ 12
Baker and Kelley (1960) ..	Norethynodrel	4 „ 20
Jolles (1962)	Hydroxyprogesterone caproate	3 „ 9
Bucalossi *et al.* (1963) ..	Medroxyprogesterone	11 „ 30
Stoll (1965)	Norethisterone acetate	
	Medroxyprogesterone	3 „ 16

Nevertheless, there still remains the evaluation of the most efficacious agent and the most suitable stage of the disease for its administration. The choice of suitable agent is made more difficult by differences in side-effects, particularly in the incidence of gastrointestinal upset, biochemical evidence of liver damage, and signs of masculinization after prolonged use. For this reason it was thought valuable for one observer, using standardized criteria, to compare examples of each class of progestin in the treatment of advanced breast cancer. This report is of a limited pilot trial of this nature.

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Material

A total of 72 postmenopausal women with advanced breast cancer were treated by synthetic oral progestins selected to represent the three major groups in use—that is, 19-nortestosterone derivatives, 17α-hydroxyprogesterone derivatives, and the testosterone derivatives. The initial daily dosage given was in general six times that used in oral contraceptive practice and is noted in Table II. Cases were not randomized, but were allocated on a chronological basis as agents became available for trial.

As well as objective evidence of tumour regression, special note was taken of side-effects from each drug—mainly the immediate ones, but also in a few cases the long-term ones. Special investigations carried out in the majority of patients included liver-function studies and serial cytohormonal assessment of the vaginal smear, both before and during treatment. In some of the later cases glucose-tolerance tests were carried out after at least four weeks of hormone treatment.

All 72 patients had undergone either a natural menopause or castration. They were suffering from advanced breast cancer, beyond the control of both surgery and radiotherapy. All patients had measurable evidence of progressing soft-tissue lesions regularly measured, and photographed when appropriate. Simultaneous treatment of the part under observation was not permitted by any method except local dressings. Patients were selected for drug trial only if the disease was progressing in activity as recorded in serial observations. Previous hormone therapy had been discontinued for at least two months and castration carried out at least six months previously.

Nathanson's (1952) classical criteria of objective response from hormone therapy in breast cancer were used. A response indicates observation of at least 50% regression in size of accessible lesions, while, at the very least, all existing inaccessible lesions remain static in activity and no new lesions appear. Of the 72 patients, there were 65 who received the hormones for two months or longer and were assessed for tumour regression. The patients who discontinued the drugs before completion of two months' treatment are excluded from the analysis as having

had insufficient trial. As this was regarded essentially as a screening trial, only patients who showed tumour regression at two months were continued on drug therapy. The earliest macroscopic regression could be identified at four weeks after starting treatment. It was maintained for periods of up to eight months when the drug was continued. Details of response for each patient are shown in Table II, and for each group in Table III.

TABLE II.—*Details of 65 Patients with Advanced Breast Cancer Assessed for Clinical Response to Progestin Therapy*

Case No.	Age	Postmenopausal (Years)	Previous Response to: Androgens	Previous Response to: Oestrogens	Progestin and Daily Dose	Response to Progestin	L.F.T. Change	Vaginal Smear: Initial	Vaginal Smear: Later	Response to Other Progestins
1	54	4		+	Norethisterone acetate 60 mg.	–		A		
2	69	17		+	,, ,,	–		I		
3	75	29	–		,, ,,	–		A		
4	71	23		–	,, ,,	–		I		
5	60	10	–	–	,, ,,	–		?		
6	81	40		+	,, ,,	+		I		
7	68	17	+	–	,, ,,	–		I		
8	54	3	+		,, ,,	–		A		
9	48	2	+	+	,, ,,	+		I		
10	48	1	–		,, ,,	–		A		
11	29	3	–	–	,, ,,	–		I		
12	44	1	+	–	,, ,,	–		I		Medroxy-progesterone –
13	52	5	–		Lynoestrenol 30 mg.	+	–	I		Lyndiol +
14	49	1			,, ,,	–	+	I		
15	65	20			,, ,,	–	+	A	I	Melengestrol –
16	48	1			,, ,,	–	+	I	I	
17	48	2			,, ,,	–	–	I		Megestrol +
18	62	9		–	,, ,,	–	–	I		Dimethisterone +
19	53	10			,, ,,	–	–	I		
20	44	1	–	–	Medroxy-progesterone 200 mg.	–		I		Norethisterone –
21	40	1		–	,, ,,	–		?	I	
22	72	24			,, ,,	–		A		
23	81	30			,, ,,	–		?		
24	48	2			,, ,,	+		I	I	
25	71	18			Medroxy-progesterone 400 mg.	–	–	I	I	Lyndiol -
26	76	26		–	,, ,,	+	–	I	I	
27	75	31		–	,, ,,	–	–	A	A	Lyndiol – Dimethisterone –
28	82	40		+	,, ,,	–	–	A	A	
29	69	21			,, ,,	–	–	A	A	Megestrol –
30	44	2			,, ,,	–	–	I	I	
31	66	18		–	,, ,,	–	–	I	A	Lyndiol –
32	66	21			Melengestrol 120 mg.	–	–	A	A	Lynoestrenol –
33	57	6		–	,, ,,	–	–	I	I	Lyndiol –
34	59	14		–	,, ,,	+	–	I	I	,,
35	84	33		–	,, ,,	–	–	I	I	
36	64	8		–	,, ,,	–	–	?	I	
37	71	26		–	Megestrol 30 mg.	–	–	I	A	
38	76	30		–	,, ,,	–	–	A	A	Dimethisterone –
39	81	40		+	,, ,,	–	–	?	I	Medroxy-progesterone –
40	48	2			,, ,,	+	–	I	I	Lynoestrenol –
41	57	11		–	,, ,,	–	–	A	A	Lyndiol +
42	45	10	–		,, ,,	+	–	I	I	
43	68	18			,, ,,	–	–	I	I	
44	68	22		+	,, ,,	–	–	I	I	
45	76	26			,, ,,	–	–	A	I	Lyndiol –
46	55	9			,, ,,	–	–	A	A	Dimethisterone – Lyndiol –
47	59	10			,, ,,	–		I		Dimethisterone +
48	71	33		–	Dimethisterone 300 mg.	Partial	–	A	A	
49	53	2			,, ,,	–	–	I	I	
50	57	15		–	,, ,,	+	–	I	I	Lyndiol +
51	62	9		–	,, ,,	+	–	I	I	Lynoestrenol –
52	42	3			,, ,,	Partial	–	A	A	Lyndiol –
53	54	8			,, ,,	,,	–	A	A	Megestrol—
54	67	17		–	,, ,,	,,	–	I	I	
55	76	30		–	,, ,,	,,	–	A	A	Megestrol –
56	45	5	–		,, ,,	+	–	A	A	
57	43	1			,, ,,	–	–	I	I	Lyndiol –
58	52	7		–	,, ,,	Partial	–	A	A	Lyndiol –
59	54	5		–	,, ,,	–	–	I	I	
60	48	1			,, ,,	Partial	–	I	I	
61	53	8			,, ,,	,,	–	I	I	Lyndiol –
62	68	24		–	,, ,,	–	–	I	I	
63	75	31		–	,, ,,	–	–	A	I	Medroxy-progesterone – Lyndiol –
64	71	25	–		,, ,,	–		?		
65	59	10		–	,, ,,	+		I		Megestrol –

A = Atrophic. I = Intermediate. ? = Inflammatory.
L.F.T. = Liver-function tests.

TABLE III.—*Agents and Dosage Used in this Trial and Clinical Response of Breast Cancer*

Progestin	Daily Oral Dose	Clinical Response in	Group Response	Significance
19-Nortestosterone Derivatives				
Norethisterone acetate	60 mg.	2 of 12	3 of 19 = 16%	Not significant
Lynoestrenol	30 ,,	1 ,, 7		
17α-Hydroxyprogesterone Derivatives				
Medroxyprogesterone ..	200–400 mg.	2 of 12	5 of 28 = 18%	
Melengestrol	120 mg.	1 ,, 5		
Megestrol	30 ,,	2 ,, 11		
Testosterone Derivative				
Dimethisterone ..	300 mg.	4 of 18	= 22%	

Results

Objective response as defined above was noted in 12 of the 65 patients. It was seen in 3 out of 19 cases on the 19-nortestosterone derivatives, in 5 out of 28 on the 17α-hydroxyprogesterone derivatives, and in 4 out of 18 on the testosterone derivative. In the last group there were 8 additional cases where the observed lesions showed regression but less than 50% reduction in size. There is no statistically significant difference in tumour response rate between the groups (Table III). However, the selected example of the testosterone derivatives (dimethisterone) differs in one respect from the other groups in that it yields a high proportion of patients with partial response, similar to that seen from corticosteroid administration (Stoll, 1963). The dose level selected for dimethisterone appears to be near its minimum effective level, as shown in four of these patients where the dosage was halved when the disease appeared to be partially under control. In two of these patients with nodular infiltration of the chest wall the symptoms of itching and tightness, which had eased at full dosage, reappeared at half dosage, but eased again when full dosage was reinstituted.

Of the 65 patients assessed for tumour response on progestins, 40 had undergone a previous trial of oestrogen or androgen therapy (Table IV). When comparing patients previously responding with those not responding to oestrogen or androgen therapy there is no statistical difference in the proportion of progestin responders (Table IV). Of eight progestin responders who had received a previous trial of oestrogens or androgens, only two had responded to these agents. It has also been reported (Stoll, 1966) that 3 out of 10 patients failing to show tumour regression on 15 mg. of stilboestrol daily did show such a regression when progestins were added. It appears, therefore, that there is no obvious correlation between tumour response to progestins and response to previous sex hormone therapy. It seems likely that progestin responders do not belong to the same group of patients as those who respond to the conventional sex hormones.

TABLE IV.—*Response to Progestins in Relation to Previous Hormonal Response*

Previous Hormone Response	Subsequently Responding to Progestins	Significance
Response to oestrogens or androgens ..	2 of 9 (22%)	Not significant
No response to oestrogens or androgens ..	7 of 31 (22%)	

Side-effects

In the total series of 72 cases, side-effects necessitated stopping therapy in seven cases, found only in the first two groups. Severe nausea and vomiting or abdominal pain accounted for five cases; in one case the complaint was of

severe mental depression and in another of irritability. Minor side-effects overcome with persistence included nausea, constipation, and backache. Breakthrough bleeding was noted in only three cases in the total series on high doses of progestins.

Unusual side-effects were noted with the selected example of the testosterone derivatives (dimethisterone). Gross increase in appetite, generally associated with a gain in weight, was mentioned by 7 of the 18 patients. In addition, four of the patients in the group noted an improvement in mood in the form of tranquillization. In two cases in this group taking the hormone for longer than five months it caused long-term side-effects in the form of puffiness of the face and hypertrichosis of the face and chin. Segaloff (personal communication, 1965) noted a Cushingoid effect from prolonged therapy with a 17α-hydroxyprogesterone derivative.

Biochemical and histological evidence of liver damage after the administration of oral progestins and oral contraceptives has been reported (Eisalo *et al.*, 1964; Stoll *et al.*, 1966). Total serum bilirubin and serum aspartate aminotransferase levels were assessed fortnightly in 45 cases in the present series. Only in the 19-nortestosterone group were abnormal changes seen in the aminotransferase levels, the first rise appearing after two weeks' drug administration. Liver biopsy carried out in one of the cases showed evidence of parenchymal cell necrosis with accumulation of lipofuscin (Stoll *et al.*, 1966). In the present series there were no cases with clinical signs of jaundice or a raised bilirubin level.

Glucose-tolerance tests were carried out in eight cases after at least four weeks' drug administration. Abnormally high blood glucose levels after one hour were noted in one of the eight cases (compared with three of four cases in a similar therapeutic trial of Lyndiol (Stoll 1967a)). The liver-function tests showed no gross abnormality in the patients with abnormal blood glucose levels.

Pretreatment Vaginal Smear

The adrenal cortex secretes androgens throughout life in the female. In addition, the secretion of oestrogens and progesterone does not cease with atrophy of the ovary at the menopause, as breakdown products of both these corticosteroids have been shown in the urine in postmenopausal women (Klopper *et al.*, 1955; Nissen-Meyer and Sanner, 1963). The major part of these corticosteroids originates in the adrenal cortex and their circulating levels are reflected in the vaginal smear. It should be noted that the distribution of vaginal smear patterns in postmenopausal patients suffering from breast cancer is no different from that of a control group of normal postmenopausal women of the same age group (Struthers, 1956; Finkbeiner, 1960).

Cytohormonal assessment of the vaginal smear was carried out before initiating treatment in all but one of the patients. After the menopause two main smear patterns are observed, an atrophic pattern and an intermediate pattern. The former indicates a complete absence of sex-hormone stimulation. The latter pattern reflects a response to adrenal hormones, but cytologists disagree on whether it reflects oestrogenic or androgenic substances or a mixture of the two.

The pretreatment vaginal smears were classified by the cytologist as atrophic if over 80% of the cells were parabasal in type, and intermediate if over 80% of cells were of the intermediate type. It is shown in Table V that whereas only 5% of patients with an atrophic smear responded to progestin therapy, 29% of patients with an intermediate smear responded. The difference is statistically significant ($P<0.03$). The pretreatment smear can therefore be used to select patients for progestin therapy in the same way that the "discriminant factor" is used before adrenalectomy or hypophysectomy in advanced breast cancer (Atkins, 1966). It is interesting that in our experience the pre-treatment vaginal smear cannot be correlated with the likelihood of a response either to oestrogens or to androgens (Stoll, 1967b).

TABLE V.—*Clinical Response to Progestins (Described in This Paper) in Relation to Initial Vaginal Smear. Parallel Figures for Lyndiol (Stoll, 1967a) for Comparison*

Hormone Therapy	Proportion of Cases Responding if Initial Vaginal Smear		Significance
	Intermediate	Atrophic	
Progestins ..	11 of 38 (29%)	1 of 21 (5%)	$P<0.03$
Lyndiol ..	8 „ 20 (40%)	1 „ 16 (6%)	$P<0.03$

Effect of Progestins on the Vaginal Smear

The 19-nortestosterone derivatives used in this trial are norethisterone acetate (17α-ethynyl derivative) and lynoestrenol (17α-ethynyl-3-deoxy derivative). Some members of this group show oestrogenic properties and, in addition, the group tends to be androgenic in experimental animals.

The 17α-hydroxyprogesterone derivatives used in this trial are medroxyprogesterone (6-methyl derivative), megestrol (6-dehydro-6-methyl derivative), and melengestrol (16-methylene derivative of megestrol). The testosterone derivative used was dimethisterone (6α,21-dimethylethisterone). These latter two groups of compounds are said to possess no inherent oestrogenicity and no significant androgenic activity in the experimental animal (Goldzieher, 1964).

Serial vaginal smear tests were carried out at two-weekly intervals during progestin therapy in 42 cases. In 16 of these patients who showed a pre-treatment atrophic pattern there was a change to the intermediate pattern in only three after the administration of progestins. One case was recorded in each of the groups—that is, the 19-nortestosterone derivatives, the 17α-hydroxyprogesterone derivatives, and the testosterone derivatives. This picture presumably reflects some degree of inherent oestrogenicity or androgenicity in the compounds involved (Table II).

Discussion

By definition, a progestational agent is one which causes a secretory response in the uterine lining after oestrogen priming. The many synthetic orally active progestational agents available have marked qualitative differences in their oestrogenicity, androgenicity, and metabolic activity. We prefer to use the term "progestins" rather than "progestogens" or "progestational agents," because their major clinical use in recent years has not been for assistance in the initiation of pregnancy. The mode of action of progestins in breast cancer may be by:

1. *Effect on Anterior Pituitary Secretion.*—There is conflicting evidence concerning the effect of progestins on total gonadotrophin excretion (Brown *et al.*, 1964). Nevertheless, it is possible that a decrease in the luteotrophin secretion alone may be the effect common to these agents (Diczfalusy, 1965). They are also said to stimulate release of mammotropin from the pituitary (Kim, 1965).

2. *Conversion of Progestins to Another Active Steroid—such as Androgen or Oestrogen.*—It is believed that some of the 19-nortestosterone derivatives have both androgenic and oestrogenic metabolites. Our vaginal smear observations suggest that this may be true of some members of the other groups also.

3. *Local Effect on the Breast Tumour.*—The possibility of a local effect by progestins on the tumour is shown by Kim's (1965) observation that in the hypophysectomized animal there is a growth-promoting effect on hormone-sensitive mammary cancer by the combined administration of oestradiol and progesterone, but not from oestrogens alone.

Recent experimental reports suggest a fourth possible mode of action. Huggins *et al.* (1962) reported a hormone-sensitive chemically induced mammary cancer in female rats. They reported that oestradiol 20 μg. daily will depress tumour

growth, but its combination with 4 mg. of progesterone daily will actually *extinguish* tumour growth in the majority. Young *et al.* (1963) noted that the administration of oestradiol after oophorectomy causes tumour reactivation in less than 50% of such rats, but the addition of progesterone causes reactivation in 95% of cases. Similarly, though Sterental *et al.* (1963) showed no reactivation of the experimental cancer by oestrogen administration after hypophysectomy, Kim (1965) noted that the combination of oestradiol and progesterone has a very potent growth-promoting effect in the hypophysectomized animal.

All these observations can be interpreted as suggesting a fourth possible mode of action of progestins in breast cancer. It is possible that progesterone acts by sensitizing experimental mammary cancer in rats to the action of oestrogens, whether in the form of stimulation or of depression of tumour growth. If this applies to man one would not expect to obtain significant response of breast cancer to progestin therapy in the absence of oestrogens. This may account for the very poor response rate seen in patients with an atrophic vaginal smear, as such a smear indicates a complete absence of oestrogen stimulation in the postmenopausal woman.

A previous paper (Stoll, 1967a) reported the effect on advanced breast cancer of Lyndiol, a commercially available oral contraceptive containing lynoestrenol, a progestin of the 19-norsteroid group, combined with the oestrogen mestranol. The proportion of responders was similar to that noted in this paper for progestin-treated cases (Table V). The addition of oestrogen (in the form and dose found in Lyndiol) does not seem to increase the response rate in the patient with an atrophic vaginal smear.

There may be some selectivity of action by particular progestins. There were five patients to whom dimethisterone was given after failure of previous progestins, and in two of them tumour response (by full criteria) was noted. However, dimethisterone given to five patients after failure of Lyndiol gave no response. It is suggested that the metabolism of different progestins might be investigated in breast cancer patients by the administration of radioactively tagged progestins. This would establish whether there is indeed a direct effect on the target organ cells. In addition, the distribution of the radioactive hormone in the tumour could be estimated by autoradiography, since localization is probably not uniform and depends on vascularity, patchy necrotic changes, or other factors.

Summary

The effect of representatives of the three major groups of progestins is compared on metastatic soft-tissue growth of breast cancer in postmenopausal women.

Objective regression of soft-tissue tumour was noted in 12 out of 65 patients treated for two months or longer. Differences in side-effects and liver toxicity between the groups are noted. In addition, a corticosteroid-like effect of one agent on breast cancer is noted.

It is possible to differentiate patients with a 29% likelihood of response from those with only a 5% likelihood of response by cytohormonal examination of the postmenopausal vaginal smear before therapy.

The possible mode of action of progestins in breast cancer is discussed.

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