A New Antifertility Factor[1]

(A Preliminary Report)

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SINCE 1949 the author has been working on an orally administered factor that promises safe and controllable antifertility activity. This work was undertaken after Beiler and Martin's (*1*) discovery of a new antihemorrhagic factor which, *in vitro* and *in vivo* in animals, had direct inhibitory action on the enzyme hyaluronidase. They found that the sulfonated and phosphorylated hespiridins inhibited materially the enzymic action of hyaluronidase. Recent reports (*2*) have specifically established a relationship of hyaluronidase to the coronal cells of the ova by a dispersion action. This action is identical with the so-called spreading factor of Duran-Reynals (*3*), which was corroborated later by McClean (*4*).

Hyaluronic acid is a mucopolysaccharide acid found in almost all animal tissues. Myer's (*5*) classic experiments showed that the gels formed by hyaluronic acid are a part of the viscous barriers that regulate the exchange of various metabolites and water. Earlier experiments (*6*) proved that at strategic points in the organism hyaluronic acid gels are disaggregated and depolymerized by the action of the enzyme hyaluronidase. This action reduces the viscosity of this "tissue cement." Myer further demonstrated that the enzyme hyaluronidase acts specifically by hydrolyzing hyaluronic acid.

It was this work that formed the basis for the hypothesis that when the hyaluronidase is in proper concentration in the cells of the spermatozoa and ovum and in the surrounding interstitial fluids, a hesperidin derivative at the proper saturation may act as an inhibitor, and this inhibitory action on the hyaluronidase occurs at the moment when the sperm comes in contact with the coronal cell layer of the ovum. It is now known (*5*) that in the presence of the hesperidin derivative the entire coronal cell layer remains intact, and, in addition, more "tissue cement" is formed, both of which surround the ovum to form an impregnable barrier to the piercing spermatozoa.

The problem of obtaining the most soluble form of hesperidin that could be administered orally or intravenously had been solved by Beiler and Martin (*7*), who showed that phosphate groups may potentiate the action of inhibitors on enzyme systems. Insofar as hyaluronidase itself is an enzyme, it was assumed that phosphorylated hesperidin would be ideal.

Martin (*8*) also proved by animal experimentation that phosphorylated hesperidin[2] was well tolerated and definitely had antifertility action.[2] In his experiments, groups of 20 male and female mice had been given doses of phosphorylated hesperidin intraperitoneally, at a level of 20 mg/kg. After one week of such daily dosage the females were exposed to the males for fertilization, while the same daily dosage was continued in the treated mice. The incidence of fertility was determined by actual deliveries. Normal males were crossed with normal females, resulting in 100 per cent pregnancy. Normal females were crossed with phosphorylated-hesperidin–treated males, with 100 per cent pregnancy. Phosphorylated-hesperidin–treated females were crossed with normal males, resulting in only 11 per cent pregnancy, and phosphorylated-hesperidin–treated females were crossed with phosphorylated-hesperidin–treated males, resulting in 11 per cent pregnancy.

To substantiate and corroborate these figures a series of animal experiments was carried out by the author, of which the following is an example.[3] Twenty male and 20 female healthy white Swiss mice, weighing 25–35 g, were selected for the experiment. The drug was administered in a solution made up from the oral tablet used clinically. Ten female and 10 male mice were given phosphorylated hesperidin in a dosage of 20 mg/kg intraperitoneally, daily for 7 days. On the eighth day, or 24 hours following final injection, mating proceeded as follows:

Group I: Five untreated females with 5 untreated males.
Group II: Four untreated females with 4 phosphorylated-hesperidin–treated males.
Group III: Six phosphorylated-hesperidin–treated females with 6 untreated males.
Group IV: Five phosphorylated-hesperidin–treated females with 5 phosphorylated-hesperidin–treated males.

Table 1 shows the percentage of pregnancies in mice treated with phosphorylated hesperidin. In this group treatment was deliberately omitted after the preliminary 7-day saturation period before mating, in order

[1] Submitted for publication Dec. 18, 1951. Originally this manuscript was prepared as a preliminary report on 50 couples from a series of more than 300. Data were brought up to date in September 1952, to include the entire group of 300 couples. A supplementary report will be published later on the time interval from delivery date to date on which control began, lactation period postpartum to concluding date of lactation, and possible effect of phosphorylated hesperidin on lactation.

[2] Only one known radical of phosphorylated hesperidin, having the correct position on the benzene ring, with a specific pH, has antifertility action. This action cannot be anticipated from just any radical of phosphorylated hesperidin.

[3] The author wishes to acknowledge the cooperation and assistance in these animal experiments, of Howard E. Lind, director, Sias Laboratories, Brooks Hospital, Brookline, Mass.

TABLE 1

PREGNANCIES IN NORMAL AND PHOSPHORYLATED-HESPERIDIN–TREATED MICE

(Medication omitted after 7 days)

	Normal males (%)	Phosphorylated-hesperidin–treated males (%)
Normal females	100	50
Phosphorylated-hesperidin–treated females	67	80

TABLE 2

PREGNANCIES IN NORMAL AND PHOSPHORYLATED-HESPERIDIN–TREATED MICE

(Medication continued through mating period)

	Normal males (%)	Phosphorylated-hesperidin–treated males (%)
Normal females	100	83
Phosphorylated-hesperidin–treated females	60	66

to provide a statistical comparison with the second group, which was treated through the saturation period and continued throughout the mating period.

The second experiment was carried out with a similar number of white mice of the same classification and weight levels. In Group I the controls remained untreated. Groups II, III, and IV were treated identically with those in the first experiment for the first 7 days. On the eighth day the females were exposed to the males for fertilization, but intraperitoneal injections in dosage of 20 mg/kg were continued daily. Table 2 shows the percentage of pregnancies in the second experiment.

Groups of 5 females in both experiments were checked for estrus cycles, which remained unchanged. Microscopic examination of the seminal fluid from males of both groups showed a normal sperm count and normal motility. Subsequent omission of phosphorylated hesperidin showed all females to be again fertile. The males, when taken off treatment and mated with normal healthy female mice, again produced 100 per cent pregnancies.

This animal evidence indicated that no permanent sterility in either sex was to be feared from phosphorylated-hesperidin therapy. This information was important in relation to anticipated work with human beings.

The discrepancies in percentage between Martin's original experiments (*8*) and ours are reconciled in the published report of Martin and Beiler (*9*). Repeated experiments are being carried out on similar groupings of white mice, but with a dose of 40 mg phosphorylated hesperidin per kilogram as the dosage level. In spite of the discrepancy between our results and Martin's, every group treated with phosphorylated hesperidin, including treated males, showed some percentage of fertility control, as compared to 100 per cent pregnancies in the untreated groups.

It can be concluded from the animal experiments that there is definite impairment of fertility of the mice under treatment with phosphorylated hesperidin. On the basis of the studies cited, it is presumed that the impairment is in the inhibition of hyaluronidase. Although the accumulated animal evidence was not as strong as desired, our previous clinical experience with hesperidin was sufficient to warrant studies in human beings.

The author had been using phosphorylated hesperidin in another clinical problem. On the basis of our own clinical experience the drug had been found to be nontoxic both to the organism and to tissues, easily assimilated, and nonaccumulative, and it caused no allergic reactions. These clinical data established the fact that for oral administration the drug could best be dispensed in 100-mg tablets. Therefore this unit of dosage suggested itself as best for the human antifertility experiments.

CLINICAL MATERIAL

This report deals with 300 couples who had been taking the new antifertility factor over varying periods, up to 30 months. The basis for selection of married couples was a history of easy impregnation and normal delivery, with the birth of at least one normal child, thereby, for all practical purposes, ruling out the question of sterility. In two cases, however, a question of sterility following one normal pregnancy and delivery did exist. The reason for including them in the study will be discussed later. Included in the group were individuals with infections, systemic diseases, traumatic injuries, and varying pathologies.

Variations in age groups represented five periods in the reproductive years. Control periods were varied for statistical study. Couples were selected not only from the author's own group of patients, but also from other groups not under his care, in order to eliminate any possible influence in the therapy given to his own patients.

No separate control group was employed in this study. The couples participating in the experiment constituted adequate controls in themselves, as shown by the fertility statistics presented in Tables 3–6. Moreover, no one could either ethically or morally ask any human couple to volunteer for a study of fertility control and then deliberately dispense placebos. Couples who had been under the author's therapy had no fear of taking this drug, as many had been taking the hesperidin factor without difficulty for 12–25 months as an antihemorrhagic factor. These couples were not fearful of pregnancy, as they were mentally and financially prepared for another pregnancy. Their faith in the author, from previous treatment, was great enough for them to say, "If you are satisfied with your animal experiments and the safety of the drug, and you know it will not cause permanent sterility, then

TABLE 3

GROUP I—43 COUPLES (14.3%) AGES 17–22 (FEMALE)

Case No. (couples)	Ages F	Ages (M)	Previous pregnancy	Total daily dosage (mg) F	Total daily dosage (mg) M	Fertility control period (months)	Fertilization time (weeks)	Pregnancy and delivery	Postpartum interval (weeks)	Secondary control period (months)	Remarks
1	17	(22)	1	350	400	6	7.5	(X)	7	12	Continuing ℞
2	19	(24)	1	350	400	3	11	(X)	4.5	13	Continuing ℞ (26-day cycle); intravenous toxicity test, 10 consecutive days up to 20 g daily
3	20	(22)	1	350	450	4	8	(X)	4	14	Continuing ℞
4	21	(23)	1	300	300	8	9	(X)	6	7	Omit ℞; ? 6 wk 3rd pregnancy (fertility period only 5 wk)
5	21	(26)	2	350	400	4	6	(X)	5	14	Continuing ℞
6	22	(25)	1	350	450	12	13	X(5)	—	—	Patient about 5 mo pregnant
7	22	(27)	2	350	400	16	—	—	—	—	Couple desire no more children; continuing ℞
8	22	(24)	1	300	450	4	7	(X)	6	14	Continuing ℞
51	17	(19)	1	300	350	7	5	X(7)	—	—	Patient about 7 mo pregnant
52	17	(20)	1	450	400	9	10	(X)(C)	8	5	Patient continuing ℞; *C* = cesarean section
53	18	(18)	1	350	350	10	10	X(4)	—	—	Patient about 4 mo pregnant
54	18	(21)	2	350	300	26	—	—	—	—	Couple desire no more children; male has cancer
55	19	(22)	1	300	300	16	7	(X)(P)	6	2	Continuing ℞; *P* = premature delivery at 8 mo
56	19	(19)	1	300	400	11	6	X(6)	—	—	Patient about 6 mo pregnant
57	19	(20)	2	300	400	8	12	(X)	4	4	Continuing ℞
58	19	(18)	1	400	350	28	—	—	—	—	Couple desire no more children; continuing ℞
59	20	(20)	3	350	450	12	8	(X)	5	3	Continuing ℞
60	20	(21)	1	300	350	7	11	(X)(P)	8	5	Continue ℞; premature delivery at 7.5 mo infant normal weight at 3 mo
61	20	(24)	2	350	400	9	5	(X)	6	4	Continuing ℞
62	20	(26)	2	300	350	6	—	—	—	—	Patient not heard from since
63	20	(25)	1	250	300	13	9	X(4)	—	—	Patient about 4 mo pregnant
64	20	(21)	1	350	400	20	7	X(9)	—	—	Patient at 9 mo is overdue 3 wk
65	21	(22)	3	400	400	18	9	X(3)	—	—	Patient about 3 mo pregnant
66	21	(20)	1	300	350	5	8	(X)	7	2	Continuing ℞
67	21	(24)	2	350	450	6	7	(X)	5	3	" "
68	21	(23)	1	300	400	15	8	X(7)	—	—	Patient about 7 mo pregnant
69	21	(26)	2	350	450	21	6	X(2)	—	—	Patient about 2 mo pregnant
70	21	(28)	3	450	300	15	—	—	—	—	Continuing ℞; couple desire no more children; tuberculosis-active
71	21	(22)	1	300	350	7	5	(X)	6	5	Continuing ℞
72	21	(23)	1	300	400	12	11	X(8)	—	—	Patient about 8 mo pregnant; mild diabetic
73	21	(24)	1	250	300	6	7	(X)	6	3	Continuing ℞
74	21	(26)	2	500	400	13	7	X(M-3)	—	—	Patient miscarried at 12 wk; bronchial asthma
75	22	(25)	1	300	350	5	8	(X)	7	2	Continuing ℞
76	22	(23)	3	400	350	11	12	X(7)	—	—	Patient about 7 mo pregnant
77	22	(23)	1	350	400	26	—	—	—	—	Continuing ℞; couple desire no more children; chronic lymphatic leukemia
78	22	(24)	3	400	350	7	5	(X)	4	5	Continuing ℞
79	22	(27)	2	300	350	18	5	X(4)	—	—	Patient about 4 mo pregnant
80	22	(27)	1	350	400	4	6	(X)	6	3	Continuing ℞
81	22	(28)	2	300	350	3	7	(X)	6	4	" "
82	22	(28)	1	350	300	14	10	X(6)	—	—	Patient about 6 mo pregnant
83	22	(29)	3	400	450	5	—	—	—	—	Patient not heard from since
84	22	(30)	1	300	400	8	6	(X)	5	2	Continuing ℞
85	22	(30)	4	300	400	23	—	—	—	—	Continuing ℞; desire no more children

we have the faith in you to go along with the experiment."

As a further assurance, a pledge was obtained from each couple that only this oral method of fertility control would be employed throughout the experiment.

All patients undergoing study were examined for possible pathological findings and nutritional status. A complete history was taken, and physical examination, urine analysis, complete blood counts, and chemistries were done.

TABLE 4

GROUP II—158 COUPLES (52.6%) AGES 23–30 (FEMALE).

Case No. (couples)	Ages F	Ages (M)	Previous pregnancy	Total daily dosage (mg) F	Total daily dosage (mg) M	Fertility control period (months)	Fertilization time (weeks)	Pregnancy and delivery	Postpartum interval (weeks)	Secondary control period (months)	Remarks
9	23	(39)	2	400	600	4.5	7	(X)	6	13	Continuing ℞
10	23	(24)	1	400	450	21	8	X(5)	—	—	Patient about 5 mo pregnant; couple toxicity study; intravenous 10 consecutive days up to 20 g daily
11	23	(26)	1	400	450	10	4	(X)	6	8	Continuing ℞; this patient was a questionable sterility case previous to therapy
12	23	(25)	1	400	500	8	7	(X)	8	9	Continuing ℞
13	24	(29)	2	400	500	15	8	X(8)	—	—	Patient about 8 mo pregnant; diabetes mellitus
14	24	(26)	1	350	400	8	7	(X)	8	8	Continuing ℞
15	24	(31)	2	400	500	6	9	(X)	5	10	" "
16	24	(28)	1	300	350	7	8	(X)	6	9	" "
17	24	(24)	1	350	400	8	6	(X)	9	9	" "
18	25	(27)	2	300	450	5	12	(X)	6	10	" "
19	25	(34)	2	350	500	8	8	(X)	5	8	" "
20	25	(30)	1	450	550	3	6	(X)	7	14	Continuing ℞; this patient was a questionable sterility case previous to therapy
21	25	(26)	1	400	450	8	7	(X)	6	9	Continuing ℞
22	25	(26)	2	450	600	13	8	X(7)	—	—	Patient about 7 mo pregnant
23	26	(27)	3	300	300	7	7	(X)	8	10	Continuing ℞
24	26	(32)	1	600	1100	3	8	(X)	6	12	Continuing ℞; high-dosage ℞ in male to be reported later
25	27	(34)	1	300	300	4	7	(X)	5	14	Continuing ℞
26	27	(28)	1	300	400	3	4	(X)	4	10	Continuing ℞; patient at 6 mo of pregnancy had virus infection, diarrhea, and vomiting
27	28	(35)	1	250	300	22	8	X(6)	—	—	Patient about 6 mo pregnant
28	28	(30)	1	350	450	6	4	(X)	6	12	Continuing ℞
29	28	(28)	2	500	550	29	—	—	—	—	Couple desire no more children; continuing ℞
30	29	(28)	1	350	450	5	7	(X)	8	11	Continuing ℞
31	29	(30)	3	350	400	8	8	(X)	6	9	" "
32	30	(33)	2	600	700	6	12	(X)	8	10	" "
33	30	(32)	3	400	450	6	7	(X)	6	11	" "
34	30	(30)	2	400	400	20	6	X(7)	—	—	Patient about 7 mo pregnant
86	23	(23)	1	250	250	6	8	(X)	6	7	Continuing ℞; normal pregnancy; mid-forceps delivery
87	23	(24)	1	300	350	10	12	X(5)	—	—	Patient about 5 mo pregnant
88	23	(26)	1	350	400	12	8	X(3)	—	—	Patient about 3 mo pregnant; weight increase too rapid, advised lower calorie diet
89	23	(27)	2	400	400	8	5	(X)	7	4	Continuing ℞
90	23	(40)	1	300	450	30	—	—	—	—	Continuing ℞; couple desire no more children; male has coronary disease
91	23	(27)	1	400	350	7	9	X(M-3)	—	—	Patient miscarried at 13 wk; to recontinue ℞ after first true menstrual period
92	23	(25)	2	350	400	5	8	(X)	6	9	Continuing ℞
93	23	(26)	3	450	400	9	7	(X)(C)	6.5	2	Continuing ℞; *C* = cesarean section; patient advised against further pregnancy
94	23	(24)	1	300	350	8	6	X(6)	—	—	Patient about 6 mo pregnant
95	23	(26)	2	400	450	6	10	X(4)	—	—	Patient about 4 mo pregnant; weight gain too rapid—advised obesity diet
96	23	(28)	2	250	350	10	8	X(3)	—	—	Patient about 3 mo pregnant; had staining past month; testosterone propionate and progesterone weekly injections; no staining past week
97	23	(26)	1	300	350	4	6	(X)	7	6	Continuing ℞; normal pregnancy; low forceps delivery
98	23	(25)	3	350	450	5	—	—	—	—	Patient not heard from since
99	23	(27)	1	250	300	7	4	X(5)	—	—	Patient about 5 mo pregnant
100	23	(29)	1	300	300	9	6	X(8)	—	—	Patient about 8 mo pregnant
101	23	(30)	2	300	400	7	10	(X)	8	3	Continuing ℞

TABLE 4—(*Continued*)

Case No. (couples)	Ages F	Ages (M)	Previous pregnancy	Total daily dosage (mg) F	Total daily dosage (mg) M	Fertility control period (months)	Fertilization time (weeks)	Pregnancy and delivery	Postpartum interval (weeks)	Secondary control period (months)	Remarks
102	24	(27)	2	300	350	27	—	—	—	—	Continuing ℞; couple desire no more children; active pulmonary tuberculosis
103	24	(25)	3	300	400	4	5	(X)	6	8	Continuing ℞
104	24	(25)	1	200	300	6	8	X(6)	—	—	Patient about 6 mo pregnant; previous history of husband being Rh +
105	24	(26)	2	250	250	9	6	X(3)	—	—	Patient about 3 mo pregnant
106	24	(27)	3	400	300	4	10	X(8)	—	—	Patient about 8 mo pregnant; overweight; diet; has subacute cholecystitis
107	24	(28)	2	350	400	7	6	(X)	7	5	Continuing ℞; normal pregnancy; mid-forceps delivery
108	24	(28)	1	400	450	5	8	(X)	6.5	6	Continuing ℞; normal pregnancy; breach delivery
109	24	(27)	2	350	300	8	5	X(4)	—	—	Patient about 4 mo pregnant
110	24	(26)	3	300	350	29	—	—	—	—	Continuing ℞; couple desire no more children
111	24	(28)	2	250	400	8	9	(X)	7	5	Continuing ℞
112	24	(27)	4	300	350	4	5	X(4)	—	—	Patient about 4 mo pregnant; past history toxemia during last 10 wk previous pregnancy
113	24	(29)	1	350	350	3	7	(X)	6	7	Continuing ℞; staining during 6th mo; received progesterone injection weekly; stopped 2 wk after first injection; went on to normal delivery
114	24	(30)	3	400	500	5	8	X(5)	—	—	Patient about 5 mo pregnant; developed diabetes insipidus 6 mo postpartum previous pregnancy
115	24	(28)	2	300	350	6	—	—	—	—	Patient not heard from since
116	24	(30)	3	400	550	10	5	(X)	8	3	Continuing ℞; patient on obesity diet
117	24	(32)	1	250	400	5	10	(X)	6	7	Continuing ℞; husband mild case of myxedema
118	25	(29)	2	300	350	19	—	—	—	—	Continuing ℞; both previous pregnancies cesarean section; has been advised against further pregnancies
119	25	(27)	1	250	300	7	5	X(6)	—	—	Patient about 6 mo pregnant
120	25	(26)	1	200	250	6	8	X(3)	—	—	Patient about 3 mo pregnant; malnutrition problem
121	25	(28)	3	350	350	8	6	(X)	7	4	Continuing ℞
122	25	(27)	2	300	400	5	7	X(5)	—	—	Patient about 5 mo pregnant
123	25	(30)	1	250	300	4	8	(X)	6	6	Continuing ℞; acute appendectomy at 8 mo, uncomplicated; normal delivery
124	25	(25)	1	450	450	7	5	(X)	7	4	Continuing ℞; both asthmatics and obese; obesity diet
125	25	(24)	4	400	350	27	—	—	—	—	Continuing ℞; couple desire no more children
126	25	(26)	1	250	300	6	4	X(4)	—	—	Patient about 4 mo pregnant
127	25	(29)	3	400	350	6	—	—	—	—	Patient not heard from since
128	25	(28)	1	300	250	9	6	X(5)	—	—	Patient about 5 mo pregnant; weight increase too rapid; obesity diet
129	25	(29)	2	300	400	8	7	(X)	5.5	2	Continuing ℞
130	25	(27)	3	400	500	5	6	X(7)	—	—	Patient about 7 mo pregnant; weight gain too rapid; obesity diet
131	25	(28)	1	300	300	10	8	X(4)	—	—	Patient about 4 mo pregnant; hypertension developed at end of 2nd mo
132	25	(30)	2	500	600	24	—	—	—	—	Continuing ℞; both obese and asthmatic; desire no more children
133	25	(32)	3	350	350	9	11	(X)	7	3	Continuing ℞; mid-forceps delivery
134	25	(31)	3	400	300	6	5	X(6)	—	—	Patient about 6 mo pregnant
135	25	(33)	1	300	450	4	8	(X)	6	5	Continuing ℞
136	26	(25)	4	250	350	7	6	X(3)	—	—	Patient about 3 mo pregnant; fracture of right clavicle beginning of 3rd month; healing well
137	26	(27)	2	300	300	25	—	—	—	—	Continuing ℞; husband was seriously injured; desire no more children

TABLE 4—(*Continued*)

Case No. (couples)	Ages F	Ages (M)	Previous pregnancy	Total daily dosage (mg) F	Total daily dosage (mg) M	Fertility control period (months)	Fertilization time (weeks)	Pregnancy and delivery	Postpartum interval (weeks)	Secondary control period (months)	Remarks
138	26	(26)	1	250	300	8	12	X(5)	—	—	Patient about 5 mo pregnant; moderate myxedema
139	26	(27)	1	450	400	5	9	(X)	6.5	4	Continuing ℞; last pregnancy delivered at 8 mo; infant normal
140	26	(27)	3	350	450	3	5	(X)	6	8	Continuing ℞; high forceps delivery
141	26	(28)	2	300	200	4	7	X(8)	—	—	Patient about 8 mo pregnant; ? toxemia: hypertension, 2+ albumen in urine, peripheral edema
142	26	(29)	1	250	350	6	10	X(4)	—	—	Patient about 4 mo pregnant; patient's infectious arthritis improved at end of second mo of pregnancy
143	26	(30)	2	350	400	7	6	(X)	7	10	Continuing ℞; patient had left pyelonephritis during 5th mo, which cleared after 6 wk; remaining pregnancy normal
144	26	(30)	3	450	550	21	—	—	—	—	Continuing ℞; because of husband's coronary condition couple desire no more children
145	26	(31)	2	300	300	6	—	—	—	—	Patient refused more pills, as she intended to become pregnant, but have heard no more since
146	26	(29)	1	300	350	4	6	X(6)	—	—	Patient about 6 mo pregnant; patient has rheumatic heart disease, with double mitral murmur
147	26	(30)	2	350	400	6	8	(X)	6	7	Continuing ℞
148	26	(28)	5	300	350	27	—	—	—	—	Continuing ℞; couple state they cannot afford more children
149	26	(31)	4	350	450	10	5	X(4)	—	—	Patient about 4 mo pregnant; male Rh negative during previous pregnancy of wife
150	26	(32)	2	400	450	9	6	(X)	7	4	Continuing ℞; patient has diabetes mellitus which flared up during 4th mo of previous pregnancy; did badly for 3 mo but developed no toxemia; high forceps delivery; advised against further pregnancy
151	26	(34)	1	350	400	5	7	(X)	8	9	Continuing ℞
152	27	(31)	2	350	350	6	—	—	—	—	Patient not heard from since
153	27	(30)	1	400	400	8	5	(X)	6	3	Continuing ℞; patient had hypertension in last 4 mo of pregnancy; normal delivery; warned against further pregnancies
154	27	(29)	3	300	400	23	—	—	—	—	Continuing ℞; couple desire no more children
155	27	(28)	3	250	350	8	8	X(5)	—	—	Patient about 5 mo pregnant
156	27	(28)	5	350	400	7	6	X(3)	—	—	Patient about 3 mo pregnant
157	27	(26)	4	350	350	5	6	(X)	5.5	7	Continuing ℞
158	27	(29)	2	300	450	7	8	(X)	6	3	Continuing ℞; patient stained 4 mo; given progesterone injections weekly; normal delivery
159	27	(29)	1	400	300	9	5	X(4)	—	—	Patient about 4 mo pregnant; weight gain too rapid; obesity diet
160	27	(30)	1	350	400	4	9	(X)	7	6	Continuing ℞
161	27	(29)	3	400	450	7	—	—	—	—	Husband killed in Korea
162	27	(31)	1	300	350	6	10	X(6)	—	—	Patient about 6 mo pregnant
163	27	(31)	2	450	400	9	7	(X)	5	4	Continuing ℞; patient obese; on diet
164	27	(32)	3	300	300	4	8	X(7)	—	—	Patient about 7 mo pregnant; stained first 4 mo; controlled on oral testosterone propionate
165	27	(33)	4	350	400	5	6	X(3)	—	—	Patient about 3 mo pregnant; has a furuncle of left labia; no glycosuria or hyperglycemia
166	27	(34)	1	400	500	9	8	X(5)	—	—	Patient about 5 mo pregnant; weight gain much too rapid; strict obesity diet

TABLE 4—(*Continued*)

Case No. (couples)	Ages F	Ages (M)	Previous pregnancy	Total daily dosage (mg) F	Total daily dosage (mg) M	Fertility control period (months)	Fertilization time (weeks)	Pregnancy and delivery	Postpartum interval (weeks)	Secondary control period (months)	Remarks
167	27	(35)	2	300	300	3	11	(X)	6	7	Continuing Rx
168	28	(31)	5	250	350	6	5	X(4)	—	—	Patient about 4 mo pregnant; patient's vitiligo flared and advanced with pregnancy
169	28	(34)	4	300	350	5	—	—	—	—	Patient not heard from since
170	28	(30)	2	350	400	8	6	X(M-3)	—	—	Patient miscarried in 12th wk; to resume Rx after first menstrual period
171	28	(30)	3	350	400	28	—	—	—	—	Continuing Rx; couple desire no more children
172	28	(29)	4	300	400	5	—	—	—	—	Patient not heard from since
173	28	(32)	2	400	450	7	8	(X)	7	5	Continuing Rx; obesity; advised obesity regime
174	28	(32)	1	300	350	5	7	(X)	6	8	Continuing Rx; low forceps delivery
175	28	(33)	2	250	300	9	6	X(6)	—	—	Patient about 6 mo pregnant; developed acute anterior poliomyelitis at 4th mo, no residual
176	28	(33)	1	400	450	6	7	(X)	8	7	Continuing Rx; patient had lobar pneumonia 5th mo; responded well to terramycin; remainder normal pregnancy; normal delivery
177	28	(33)	4	350	400	5.5	—	—	—	—	Patient not heard from since
178	28	(34)	2	300	450	7	5	(X)	6	4	Continuing Rx
179	28	(36)	1	400	500	4	8	X(7)	—	—	Patient about 7 mo pregnant; weight gain too rapid; obesity diet
180	28	(36)	4	300	400	10	6	X(3)	—	—	Patient about 3 mo pregnant
181	28	(34)	3	350	350	8	4	(X)	5	3	Continuing Rx
182	28	(31)	2	400	400	23	—	—	—	—	Continuing Rx; couple desire no more children
183	28	(35)	1	350	450	5	6	(X)	5.5	8	Continuing Rx
184	29	(29)	3	450	550	9	5	(X)	7	2	Continuing Rx; obesity regime
185	29	(30)	1	300	450	6	8	(X)	6	7	Continuing Rx; patient premature delivery at 8 mo; infant normal at 4 mo
186	29	(30)	5	350	300	3	4	X(5)	—	—	Patient about 5 mo pregnant; advised against further pregnancies
187	29	(33)	3	400	350	12	6	X(3)	—	—	Patient about 3 mo pregnant; has acute glomerular nephritis; watch closely
188	29	(31)	2	350	450	8	6	(X)	7	3	Continuing Rx
189	29	(34)	1	300	400	4	8	X(4)	—	—	Patient about 4 mo pregnant; nausea first 3 mo; controlled with B_6 injections biweekly
190	29	(27)	1	250	350	6	5	X(8)	—	—	Patient about 8 mo pregnant; membranes ruptured and draining watery discharge past 3 days
191	29	(35)	5	400	500	28	—	—	—	—	Continuing Rx; couple desire no more children
192	29	(33)	1	350	450	26	—	—	—	—	Continuing Rx; husband has carcinoma of colon; wife has pernicious anemia, controlled; couple desire no more children
193	29	(31)	6	300	350	4	7	X(6)	—	—	Patient about 6 mo pregnant; advised to go under constant Rx after this delivery
194	29	(35)	2	500	600	5	6	(X)(C)	7.5	5	Continuing Rx; *C* = cesarean section; obesity regime for both
195	29	(37)	3	300	400	3	5	X(3)	—	—	Patient about 3 mo pregnant; male has active pulmonary tuberculosis
196	29	(37)	2	300	300	4	8	(X)	6	4	Continuing Rx; previous delivery by low forceps
197	29	(35)	5	350	400	8	5	X(4)	—	—	Patient about 4 mo pregnant; patient had rubella at 2nd mo of pregnancy; no complications
198	29	(37)	1	400	500	7	9	(X)	7	2	Continuing Rx; male mild diabetic; on obesity-reducing regime
199	29	(37)	3	300	350	6	—	—	—	—	Wife killed in automobile accident
200	29	(39)	2	350	400	23	—	—	—	—	Continuing Rx; couple desire no more children

TABLE 4—(*Continued*)

Case No. (couples)	Ages F	Ages (M)	Previous pregnancy	Total daily dosage (mg) F	Total daily dosage (mg) M	Fertility control period (months)	Fertilization time (weeks)	Pregnancy and delivery	Postpartum interval (weeks)	Secondary control period (months)	Remarks
201	29	(39)	1	250	350	9	6	X(3)	—	—	Patient about 3 mo pregnant; patient mild diabetic, controlled
202	30	(33)	4	350	400	22	—	—	—	—	Continuing ℞; couple desire no more children
203	30	(31)	7	500	450	14	8	X(4)	—	—	Patient about 4 mo pregnant; on obesity diet; male has severe myxedema; advised continuous ℞ after delivery
204	30	(32)	2	500	600	5	5	(X)(C)	8	4	Continuing ℞; *C* = cesarean section; obesity regime for both
205	30	(33)	3	400	500	20	—	—	—	—	Continuing ℞; patient has anterior pituitary mixed tumor; couple desire no more children
206	30	(36)	1	350	350	7	6	X(5)	—	—	Patient about 5 mo pregnant
207	30	(38)	5	300	400	6	—	—	—	—	Patient not heard from since
208	30	(37)	2	350	500	4	8	(X)	6	3	Continuing ℞
209	30	(38)	1	300	450	9	5	(X)	7	6	" "
210	30	(39)	4	400	450	5	6	(X)	6.5	6	" "
211	30	(40)	2	450	500	20	—	—	—	—	Continuing ℞; couple desire no more children; both on obesity regime
212	30	(36)	1	350	450	8	7	(X)	6	3	Continuing ℞
213	30	(40)	5	400	200	6	6	X(3)	—	—	Patient about 3 mo pregnant; male has carcinoma of prostate, controlled
214	30	(41)	4	350	550	18	—	—	—	—	Continuing ℞; couple desire no more children
215	30	(39)	2	300	350	7	11	(X)	8	4	Continuing ℞
216	30	(36)	3	350	450	26	—	—	—	—	Continuing ℞; couple desire no more children
217	30	(40)	1	300	400	5	8	X(6)	—	—	Patient about 6 mo pregnant; male has Rh negative blood

Daily therapeutic requirements were estimated in proportion to the weight level of the individual. Dosage was based on a unit of 5 mg of phosphorylated hesperidin for each kilogram of body weight, with an excess allowance to protect against possible loss through faulty absorption or excessive elimination. For example, a patient weighing 150 pounds (68 kg) would require 5 times 68, equal to 340 mg. The dosage given such a patient was 500 mg in divided doses—that is, 2 tablets of 100 mg each at breakfast, 1 tablet of 100 mg at lunch, and 2 tablets of 100 mg each at dinner. Earlier clinical experience had proved that concentration of the drug in the blood stream was a pertinent factor, and that a single daily dose would not maintain saturation. Because of the results obtained from animal experiments cited above, as well as from certain clinical experience to be described later, it was decided to administer medication to both male and female. All couples were therefore instructed emphatically that distribution of dosage with meals was essential if proper saturation was to be obtained. They were further advised that the medication must be taken by both male and female for 10 consecutive days to be certain of sustained adequate blood levels, in order that the antifertility effect could be assured. Also because of our clinical experience, they were cautioned that omission of medication by either partner for 48 hours would necessitate another consecutive 10-day period before antifertility action could be reestablished.

Although previous experience had indicated the nontoxicity of the drug, patients in the earlier groups who received more than 300 mg/24 hours were carefully watched for toxic symptoms. Particular attention was paid to blood changes, effects on the cardiorespiratory system, hepatic, renal, and metabolic functions, skeletal changes, bowel action, sleeping habits, nervousness, and irritability. The nontoxicity of the drug was further substantiated when a group of 15 couples, who had received up to 25 times the required oral dosage over a 10- to 50-day period, showed no toxic effects of any kind. Of this group of 15, five couples were given the drug intravenously in physiological saline solution, by the Murphy drip method, over 24-hour periods, two of the group receiving as much as 20,000 mg (20 g) in 24 hours for 10 consecutive days. No toxic manifestations or allergic reactions of any kind were encountered in any of these clinical studies.

The question of a clinical test that would serve as a guide in the administration of the drug was the next problem. Aside from saturation in the blood stream, no satisfactory test was found for the female. In the male, however, studies were made on fresh ejaculations for the presence of the enzyme hyaluronidase. The

TABLE 5

GROUP III—65 COUPLES (21.7%) AGES 31–37 (FEMALE)

Case No. (couples)	Ages		Previous pregnancy	Total daily dosage (mg)		Fertility control period (months)	Fertilization time (weeks)	Pregnancy and delivery	Postpartum interval (weeks)	Secondary control period (months)	Remarks
	F	(M)		F	M						
35	31	(30)	3	500	600	3	8	(X)	6	14	Continuing ℞; both overweight; put on obesity regime
36	31	(35)	1	450	450	16	8	X(5)	—	—	Patient about 5 mo pregnant; stained first 2 mo; controlled progesterone biweekly, parenterally
37	31	(33)	1	300	400	28	—	—	—	—	Continuing ℞; couple desire no more children
38	32	(35)	2	350	600	7	7	(X)	5	10	Continuing ℞; male hypertensive
39	32	(36)	1	450	500	8	8	(X)	6	9	Continuing ℞; obesity regime for both
40	33	(40)	1	450	600	21	4	X(4)	—	—	Patient about 4 mo pregnant; has hypertension; obesity regime for both
41	33	(38)	2	400	450	6	8	(X)	6	11	Continuing ℞
42	34	(35)	3	250	300	6	7	(X)	8	10	Continuing ℞; patient had bronchopneumonia 5th mo of pregnancy; responded to penicillin, aureomycin combination
43	36	(36)	2	400	500	4	8	(X)	5	13	Continuing ℞; high forceps delivery
44	37	(44)	3	400	400	28	—	—	—	—	Continuing ℞; male had cerebral accident; couple desire no more children
218	31	(32)	1	300	300	10	6	X(6)	—	—	Patient about 6 mo pregnant
219	31	(32)	2	250	300	7	5	(X)	6	10	Continuing ℞; low forceps delivery
220	31	(33)	2	400	500	8	7	(X)	12	7	Continuing ℞; obesity regime for both
221	31	(34)	3	350	400	29	—	—	—	—	Continuing ℞; male had acute coronary thrombosis; couple desire no more children
222	31	(33)	1	300	350	9	6	X(2)	—	—	Patient about 2 mo pregnant; ? staining past 2 wk; preventive parenteral testosterone propionate and progesterone biweekly
223	31	(35)	3	350	450	5	8	(X)	5	11	Continuing ℞
224	31	(37)	4	300	350	6	—	—	—	—	Patient not heard from since
225	31	(36)	2	350	350	8	8	X(4)	—	—	Patient about 4 mo pregnant; patient has hypertension, increased past mo
226	32	(35)	1	300	350	7	6	(X)	6	8	Continuing ℞; patient had staining 1st 3 mo, in previous pregnancy; controlled oral testosterone propionate; breach delivery
227	32	(35)	2	250	350	28	—	—	—	—	Continuing ℞; patient is severe hypertensive; couple desire no more children
228	32	(35)	3	300	400	24	6	X(3)	—	—	Patient about 3 mo pregnant; previous delivery was a placenta praevia
229	32	(37)	1	250	300	16	4	(X)(C)	11	2	Continuing ℞; *C* = cesarean section; advised to have no more pregnancies
230	32	(38)	2	400	350	5	—	—	—	—	Patient not heard from since
231	32	(39)	1	300	400	10	6	X(6)	—	—	Patient about 6 mo pregnant; fractured left wrist in 2nd mo; well-healed
232	32	(38)	3	350	350	9	8	(X)	6	7	Continuing ℞; patient has acute cholecystitis attacks
233	32	(31)	4	300	300	11	5	(X)	5	6	Continuing ℞; patient had lobar pneumonia 1st mo of pregnancy; responded to terramycin
234	33	(34)	2	350	450	12	6	X(5)	—	—	Patient about 5 mo pregnant
235	33	(40)	5	350	300	26	—	—	—	—	Continue ℞; patient has severe arthritis deformans; desires no more children
236	33	(33)	1	300	350	13	7	(X)	6	4	Continuing ℞
237	33	(35)	1	250	350	7	8	X(3)	—	—	Patient about 3 mo pregnant
238	33	(35)	3	350	300	5	6	(X)	5	10	Continuing ℞; patient has rheumatic heart disease, mitral regurgitation, aortic stenosis; well-compensated
239	33	(36)	2	300	400	11	8	X(7)	—	—	Patient about 7 mo pregnant

TABLE 5—(*Continued*)

Case No. (couples)	Ages F	Ages (M)	Previous pregnancy	Total daily dosage (mg) F	Total daily dosage (mg) M	Fertility control period (months)	Fertilization time (weeks)	Pregnancy and delivery	Postpartum interval (weeks)	Secondary control period (months)	Remarks
240	33	(30)	4	250	300	12	**6**	(X)	4	5	Continuing ℞; patient had acute anterior poliomyelitis, 4th mo preganacy; left with no residual
241	34	(35)	2	300	350	**9**	**7**	(X)	5	7	Continuing ℞
242	34	(37)	4	350	400	13	**6**	X(5)	—	—	Patient about 5 mo pregnant; had acute left pyelonephritis, beginning 4th mo
243	34	(39)	3	300	350	**5.5**	—	—	—	—	Patient not heard from since
244	34	(38)	2	250	300	13	6	X(3)	—	—	Patient about 3 mo pregnant; has mild Simmonds' disease
245	34	(38)	5	300	400	17	—	—	—	—	Continuing ℞; patient has severe diabetes mellitus; desires no more children
246	34	(39)	1	350	300	**14**	**8**	(X)	4	3	Continuing ℞
247	34	(40)	1	300	400	4	**6**	(X)(P)	5	4	Continuing ℞; patient delivered prematurely 8th mo by high forceps; infant normal weight 3rd mo
248	34	(41)	2	400	350	21	—	—	—	—	Continuing ℞; couple desire no more children
249	35	(35)	4	300	300	16	12	X(7)	—	—	Patient about 7 mo pregnant; has pernicious anemia, controlled, with B_{12}
250	35	(36)	3	300	400	15	8	X(4)	—	—	Patient about 4 mo pregnant
251	35	(37)	2	350	350	20	—	—	—	—	Continuing ℞; can afford no more children
252	35	(39)	1	300	300	10	7	(X)	6	3	Continuing ℞; delivery by version
253	35	(40)	1	250	300	4.5	—	—	—	—	Both killed in automobile accident
254	35	(40)	2	300	350	5	6	(X)	5	4	Continuing ℞
255	35	(39)	3	350	300	12	11	X(8)	—	—	Patient about 8 mo pregnant; has had bleeding duodenal ulcer 5 mo
256	35	(41)	5	300	400	15	4	X(5)	—	—	Patient about 5 mo pregnant; male has severe diabetes mellitus, controlled; advised continuous ℞ after this pregnancy
257	36	(40)	2	350	300	4	10	(X)	6	5	Continuing ℞
258	36	(51)	1	300	350	3	6	(X)	5	6	Continuing ℞; male has carcinoma of tongue
259	36	(39)	2	400	500	10	8	X(4)	—	—	Patient about 4 mo pregnant; has mild hypertension; slight increase past mo
260	36	(40)	3	300	350	9	9	X(7)	—	—	Patient about 7 mo pregnant; staining for 10 wk beginning of 3rd mo; parenteral progesterone biweekly
261	36	(39)	4	300	400	18	—	—	—	—	Continuing ℞; patient has severe diabetes mellitus; desire no more children
262	36	(38)	3	350	300	7	**6**	(X)	4	4	Continuing ℞
263	36	(40)	2	400	450	8	5	(X)	6	7	Continuing ℞; both on obesity regime
264	36	(39)	2	300	400	6	—	—	—	—	Patient not heard from since
265	37	(43)	1	350	450	5	6	(X)	5	8	Continuing ℞; patient had pertussis 2 mo previously
266	37	(41)	1	400	450	8	12	X(6)	—	—	Patient about 6 mo pregnant; had acute appendectomy 3rd mo pregnancy; recuperated quickly
267	37	(45)	1	300	350	14	—	—	—	—	Continuing ℞; couple desire no more children
268	37	(43)	2	350	400	12	8	X(5)	—	—	Patient about 5 mo pregnant; appendectomy 2nd mo; no complications
269	37	(44)	1	300	300	8	10	(X)	5	7	Continuing ℞; delivery mid-forceps; bad varicosities of legs
270	37	(42)	3	300	350	5	—	—	—	—	Patient not heard from since
271	37	(42)	1	350	400	9	6	X(2)	—	—	Patient about 2 mo pregnant; history toxemia last 3 mo of 1st pregnancy
272	37	(48)	1	250	300	11	—	—	—	—	Continuing ℞; male has bronchiogenic carcinoma of lung (right); couple desire no more children

usual studies were made: sperm count, percentage motility, percentage morphology, and total volume. An estimate of hyaluronidase in turbidity-reducing units (TRU) after the method of Nodine and Perloff (*10*)

TABLE 6

GROUP IV—19 COUPLES (6.3%) AGES 38–40 (FEMALE)

Case No. (couples)	Ages F	Ages (M)	Previous pregnancy	Total daily dosage (mg) F	Total daily dosage (mg) M	Fertility control period (months)	Fertilization time (weeks)	Pregnancy and delivery	Postpartum interval (weeks)	Secondary control period (months)	Remarks
45	38	(37)	1	350	600	6	7	(X)	5	11	Continuing ℞
46	39	(40)	3	450	500	7	11	(X)	12	6	Continuing ℞; low forceps delivery; patient has hypertrophic and infectious arthritis
47	40	(45)	1	350	450	16	—	—	—	—	Continuing ℞; couple desire no more children
48	40	(51)	2	600	800	8	8	(X)	6	5	Continuing ℞; both on obesity regime
273	38	(39)	3	300	350	29	—	—	—	—	Continuing ℞; couple desire no more children
274	38	(41)	5	350	350	25	—	—	—	—	Continuing ℞; severe arthritis; couple desire no more children
275	38	(45)	1	300	400	10	12	(X)	5	6	Continuing ℞
276	38	(47)	3	350	300	28	—	—	—	—	Continuing ℞; couple desire no more children
277	38	(49)	2	400	450	8	6	X(6)	—	—	Patient about 6 mo pregnant; stained 1st 2 mo; control oral testosterone propionate
278	39	(43)	1	350	400	8	9	(X)	4	9	Continuing ℞; acute pleurisy (left) 6th mo of previous pregnancy
279	39	(37)	1	300	350	24	—	—	—	—	Continuing ℞; patient burnt in holocaust
280	39	(44)	2	350	400	6	—	—	—	—	Patient not heard from since
281	39	(47)	1	350	350	26	—	—	—	—	Continuing ℞; couple desire no more children
282	39	(50)	1	400	500	5	7	(X)	6	10	Continuing ℞; delivered by low forceps
283	40	(41)	3	450	400	7	8	(X)	6	8	Continuing ℞; moderate diabetes mellitus, controlled
284	40	(44)	2	300	350	11	6	X(5)	—	—	Patient about 5 mo pregnant; mild diabetic; controlled on diet
285	40	(46)	4	350	400	30	—	—	—	—	Continuing ℞; couple desire no more children
286	40	(49)	2	300	350	8	11	X(4)	—	—	Patient about 4 mo pregnant; has acute cholecystitis
287	40	(51)	2	400	450	29	—	—	—	—	Continuing ℞; couple desire no more children
						GROUP V—15 COUPLES (5%) AGES 41–43 (FEMALE)					
49	41	(44)	2	600	500	29	—	—	—	—	Continuing ℞; couples desire no more children
50	43	(49)	4	250	250	30	—	—	—	—	
288	41	(42)	3	300	350	20	—	—	—	—	
289	41	(40)	2	350	400	23	—	—	—	—	
290	41	(43)	4	400	500	23	—	—	—	—	
291	41	(46)	3	500	550	25	—	—	—	—	
292	41	(50)	1	450	400	17	12	X(7)	—	—	Patient about 7 mo pregnant; severe bronchial asthmatic
293	42	(51)	5	500	600	25	—	—	—	—	Continuing ℞; couples desire no more children
294	42	(51)	3	450	500	26	—	—	—	—	
295	42	(52)	6	300	400	26	—	—	—	—	
296	42	(53)	2	400	500	27	—	—	—	—	
297	43	(54)	1	400	450	27	—	—	—	—	
298	43	(54)	5	500	600	28	—	—	—	—	
299	43	(55)	4	400	500	28	—	—	—	—	
300	43	(58)	3	350	450	29	—	—	—	—	

was recorded. This study in itself was extremely interesting and explains some of the discrepancies found in the animal experiment. However, discussion of these findings involves extensive material that cannot be included in the present communication; it will be reported completely in a subsequent publication.

A comparative study was made of the incidence of coitus before and during therapy. On questioning the female, one significant fact was revealed. Many of those who had been using mechanical devices showed a definite increase in total orgasm when the oral therapy was used. From this observation it may be deduced that mechanical methods had produced a state of anxiety causing varying degrees of frigidity, which

resulted in a loss of total orgasm. A significant increase in the frequency of coitus was found in this group. Interestingly enough, it was discovered that the frequency pattern now practiced by these couples corresponded essentially to the frequency pattern practiced in the early months of their marriage.

Statistical Case Analysis

The 300 couples reported are divided into five age groups according to the reproductive years. The age of the female provides the basis for classification. Of this group:

I. 43 couples (14.3%) varied in age from 17 to 22 years (Table 3).
II. 158 couples (52.6%) varied from 23 to 30 years (Table 4).
III. 65 couples (21.7%) varied from 31 to 37 years (Table 5).
IV. 19 couples (6.3%) varied from 38 to 40 years (Table 6).
V. 15 couples (5%) varied from 41 to 43 years (Table 6).

In Group I, 25 couples have had 1 normal pregnancy with normal delivery and normally developed child; 11 have had 2 normal children; 6 have had 3; 1 has had 4. In Group II, 59 couples have had 1 normal child; 47 have had 2 children; 29 have had 3; 13, 4; 8, 5; 1, 6; and 1 has had 7. Of Group III, 22 couples have had 1 child; 20 have had 2 children; 14, 3; 6, 4; 3, 5. Of Group IV, 7 couples have had 1 normal child; 6 have had 2 children; 4, 3; 1, 4; and 1 has had 5. Of Group V, 2 couples have had 1 child; 3 have had 2; 4, 3; 3, 4; 2, 5; and 1 has had 6. The interval from the end of the last postpartum to the beginning of the fertility control period varied from 2 to 21 months. Breast-fed infants averaged 25.2 per cent. Periods of breast-feeding varied from 2 weeks to 6 months.

All couples who terminated fertility control did so voluntarily for the purpose of having a wanted child, with the exception of three cases, which will be discussed later. The shortest period of fertility control was 3 months; the longest period was 30 months. Of the entire group of 300 couples, 21 females from Group I, 69 from Group II, 27 from Group III, and 6 from Group IV (total 123, 41 per cent) have had a period of fertility control followed by a normal pregnancy, and repeated therapy for a second period of control after the first menstrual period postpartum. Secondary periods of fertility control varied from 2 to 14 months. Ninety-seven couples (32.3 per cent) have gone through a period of control and are now in varying stages of pregnancy. Of these there were 14 in Group I, 57 in Group II, 21 in Group III, 4 in Group IV, and 1 in Group V. Sixty couples (20 per cent) were controlled continuously up to 30 months. The remaining 20 couples (6.7 per cent) were controlled for periods up to 6 months but were not heard from thereafter.

The total woman-years of protection for the 300 cases was 317.1—247.6 in the first control period and 69.5 in the secondary control period. The two control periods, giving the grand total of 317.1 woman-years, yield a figure far above the American Medical Association standard of 200 woman-years for any group studied for 12 months.

No couple in the entire group of 220 pregnancies reported any difficulty in impregnation. The longest period required for conception was 9–13 weeks, of which there were 31 cases; 179 couples reported a 5- to 8-week interval, and 10 reported impregnation after the first menstrual period following omission of medication. The incidence of miscarriage, premature births, and cesarean section was as follows: 3 miscarriages at 12–13 weeks; 5 premature births at 7½–8 months; and 5 cesarean sections. All other pregnancies, deliveries, and postpartum periods were normal. Babies born to these couples were all healthy, normal specimens. Breast-fed babies averaged 39.5 per cent. Periods of breast-feeding varied from 4 weeks to 6 months.

Two couples who had experienced a long period of questionable sterility prior to this therapy surprisingly fell into the group of 10 cases requiring but one cycle for impregnation. As mentioned previously, they had been deliberately selected for the experiment because of their history of one normal child, followed by a long period of apparent sterility, although both husband and wife had been declared normally fertile by competent urologists and obstetricians. Apparently some correction may have occurred, which suggests the possibility that phosphorylated hesperidin may possess fertility-stimulating, as well as antifertility, activity. However, further study is essential before a definite explanation can be elicited.[4]

Discussion and Conclusions

In the present study of 300 married couples the antifertility action of the drug was complete except for the two cases described. The two so-called failures are of no scientific significance, because of the lack of cooperation of the couples, as revealed by our method of dispensing medication. The tablets were bottled in lots of 100, each bottle recorded on a tally card for the patient to whom it was given, with the date and dosage for that patient. No one but members of the office staff dispensed the tablets. When a patient applied for more tablets he was required to return any remaining from the previous lot. Before more tablets were dispensed, a tally was made against the previous date and daily dosage. The number of tablets returned plus the number calculated should be equal to the total number dispensed for that period.

For example, in tallying the intake of the first so-called failure, there was a discrepancy of 200 tablets in the male and 160 tablets in the female. This was consistent with a 40-day dosage of 500 mg/24 hours for the husband, and 40 days at 400 mg/24 hours for the wife. Confronted with this information, the couple ad-

[4] Since writing this report an additional case has been seen —that of a 26-year-old female who had been having anovulatory cycles—which seems to fall into this possible group. Observations on these cases will be reported in a later communication.

mitted they had not taken their medication during a 40-day Rocky Mountain tour. The second failure showed a discrepancy of some 110 tablets, and upon careful questioning the couple admitted that during a drinking spree lasting 7 days neither member had followed the prescribed therapy.

Eighteen other patients in this group of 300 showed discrepancies varying up to 46 tablets in one individual—the male member of one couple. These omissions, however, were sporadic over a 90-day period, during which not more than 2 tablets had been omitted in any 24-hour period. The remaining tablets were accounted for by irregular omissions of not more than one 100-mg tablet from a total of 600 mg in a 24-hour period. Instructions were followed precisely by the remaining 280 cases, resulting in a 100 per cent check of all tallies.

The necessity of divided dosage over a 24-hour period has been mentioned. This was important to establish a blood saturation level, which remained fairly constant over a 24-hour period. Experience has proved that the drug is best administered with meals; where necessary, a fourth dose can be given at bedtime. The author's general rule was to prescribe four doses for the wife, and three doses for the husband during the 24-hour period. A constant observation in all couples taking this medication was the lack of rebellion against taking the medication in divided doses. Patients who have been opposed to taking pills all their lives seemed willing to take this factor. It is most important to impress upon the couples this distribution of dosage, as success depends upon the blood saturation.

This drug is an oral medication, physiological in action, which can be taken indefinitely without toxic effects or permanent inhibition of fertility. The medication must be taken for 10 consecutive days by both partners before antifertility action can be assured, and thereafter continuously by both partners at the prescribed daily divided dose. Fertility can be restored merely by omitting the drug for a 48-hour period. Should medication be omitted for 48 hours by either member of the couple, the 10 consecutive days of therapy must be repeated by both partners in order to re-establish fertility control. Following pregnancy, these 10 consecutive days of medication should not be started until after the first menstrual period postpartum. Phosphorylated hesperidin has been given clinically along with other substitution factors, such as vitamins, endocrines, amphetamine derivatives, and decholic acid derivatives without apparent interference in its action. As has been shown in both the text and tables, its antifertility action is not inhibited by trauma, infectious diseases, or systemic diseases. Again a word of warning must be expressed—it must be remembered that only one specific radical of this drug, phosphorylated hesperidin, has antifertility activity.

It must be realized that this preliminary report is presented for its experimental value only. Much more clinical data must be accumulated before the general use of this antifertility factor is warranted.

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News and Notes

Symposium on Phosphorus Metabolism, Part II

THE second Symposium on Phosphorus Metabolism, sponsored by the McCollum-Pratt Institute, was held at The Johns Hopkins University, Baltimore, June 16–19, 1952. Part I of this symposium was held a year ago, and this sequel provided an opportunity for discussion of those aspects not covered or only briefly treated in Part I.

The program started with a discussion of Phosphate Assimilation, with formal presentations by D. M. Greenberg, who covered the animal metabolic aspect, and by P. K. Stumpf, who dealt with plant metabolism. The second session considered the Role of Phosphate in Amino Acid and Protein Metabolism, and formal papers were presented on the following subjects: Enzymatic Synthesis of Glutathione, by K. Bloch; Transpeptidation and Transamidation Reactions, by C. S. Hanes; Synthesis and Transfer of Labile Methyl Groups, by G. Cantoni; Genetic Control of Enzyme Formation, by D. Bonner; and Enzymatic Dephosphorylation of Phosphoproteins and the Nature of Phosphorus Linkages, by G. Perlmann. Session III, dealing with the Role of Phosphorus in the Metabolism of Lipids, consisted of papers on The Chemistry of Phospholipids, by J. Folch-Pi; Formation of Phospholipids in Animal Tissues, by C. Artom, and The Enzymatic Oxidation of Fatty Acids, by E. D. Kennedy. The Chemistry and Metabolism of Nucleic Acids, the topic for Session IV, included the follow presentations: The Products of Nucleic Acid Hydrolysis and their Relationship to its Structure, by E. Volkin; Newer Aspects of the Chemistry of Nucleic Acids, by S. Zamenhof; Metabolism of Nucleic Acids in Microorganisms, by J. O.