that there was no lysis.

The anti-lytic effect of chicken plasma used in culturing mammalian tumors has been established by other investigators. Gey and Gey[6] have reported that the use of a large amount of chicken plasma helped to prevent early liquefaction, but sometimes delayed growth. A strain of sarcoma cells derived from a dibenzanthracene mouse tumor was cultured *in vitro* for more than two years by Jacoby,[10] with almost no liquefaction of the chicken plasma clot. The supernatant consisted of chicken serum, chicken embryo juice and Tyrode solution. Lewis and Strong,[11] in a survey of over 50 different spontaneous mouse tumors in tissue culture, found that the cultures rapidly liquefied the clot when it was composed of mouse plasma or a mixture of mouse and chicken plasma. In chicken plasma, however, such liquefaction did not occur.

In assigning the profibrinolysis to the serum and the kinase to the cells we are following the current ideas of Christensen and McLeod.[7,12] Our data are not such as to eliminate the inverse possibility: profibrinolysin in the tissue activated by a blood kinase. We cannot assume that there are differences only in the amount of profibrinolysin of various animal sera. There may be differences in the amounts of activator released by the cells of animals of different orders, since Fleisher and Loeb,[4] and Astrup and Permin[5] have reported differences in the lytic activity of tissues from various animals.

Summary. 1. Mouse Sarcoma 180 cells, in the presence of mammalian serum, cause lysis of chicken plasma clots. 2. Mammalian aqueous humor has slight influence on the fibrinolytic process. 3. When Sarcoma 180 is grown in the presence of avian serum, no lysis occurs. If a sufficient quantity of chicken serum is added to a supernatant fluid containing mammalian serum there is a decrease in the amount of clot lysis. 4. Lysis of the plasma clot by Sarcoma 180 does not occur when mammalian serum previously heated to 56°C for 3 hours is used, or when all serum is omitted from the supernatant. 5. The different degrees of lysis obtained when sera from various mammalian orders are used may be due to differences in the amount of profibrinolysin contained in the various sera. 6. There are two factors necessary for the lytic mechanism, tentatively classified as a profibrinolysin from the serum, and an activator of the profibrinolysin derived from the tissue.

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16169

Dichotomy Between Hypophyseal Content and Amount of Circulating Gonadotrophins During Starvation.*

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The amounts of gonadotrophin contained within the pituitary gland have often been assumed to parallel the amount produced and released into the blood stream. Since the gonadotrophic hormone content of the hypophysis must be the resultant of the amounts produced and the amounts released, they do not necessarily parallel each other. It is the purpose of this investigation to assess the effect of acute starvation on pituitary gonadotrophic hormone content and its release into the circulation.

The effective amount of circulating gonad-

* Supported in part by a grant from the Eli Lilly Company through the courtesy of Dr. D. C. Hines.

otrophins appears to drop markedly during starvation as judged by ovarian atrophy, uterine atrophy, and anestrus vaginal smears in rodents,[1–7] and amenorrhea in women. The target organ atrophy is not due to a refractory state of the ovaries but to absence of gonadotrophins. This is suggested by the capacity of the ovaries of starved rodents to respond to injections of gonadotrophins[1,3,4,6,7] and the reduced urinary gonadotrophin output in women.[8,9]

Hypophyseal content of gonadotrophins has been determined in chronically starved rats and found to be decreased by Mason and Wolfe[2] and Werner[4] and not changed from normal by Marrian and Parkes.[1] In more acutely starved rats Pomerantz and Mulinos[10] could detect no decrease from normal. Each group of investigators used the method of implanting entire pituitary glands into the recipient assay rats. Since, following implantation, necrosis, growth and elaboration, or encapsulation may occur, the delivery of gonadotrophic hormone is exceedingly variable. This alone may account for the divergent results reported.

Methods. Adult (5 months old) Sprague-Dawley female rats were divided into three groups: Control rats fed *ad libitum;* rats starved for 12 days; and rats starved for 12 days and injected with a suspension of rat

TABLE I.

	Donor rats							Recipient assay rats			
		Body weight						Uterine wt, mg			
Procedure	No. rats	Before g	After g	% change	Ant. Pituit. wt, mg	Uterine wt, mg	Ovarian wt, mg	Vaginal smears	with fluid	without fluid	Ovary wt, mg	No. rats
Controls fed *ad lib.*	7	219	229	+5	9.7	501	63.0	cycling	175	110	21.3	7
Starved 12 days	5	223	142	—36	6.1	195	30.3	atrophic in 4 days (2-6 days)	321	152	28.2	5
Starved 12 days, RAP* days 9 to 11	6	222	137	—38	9.6	368	73.0	cornified following RAP inj.	302	145	20.2	6
								Uninj. assay rats	41	41	15.6	9
Controls fed *ad lib.*	5	257	261	+2	12.5	646	67.1	—	225	130	13.0	5
Starved 16 days	7	253	156	—38	8.6	202	26.1	—	248	124	14.5	7
								Uninj. assay rats	42	42	13.5	10

* Rat anterior pituitary gland suspensions, derived from rats castrated 10 months previously, were injected twice daily for 3 days, a total of ½ gland per rat.

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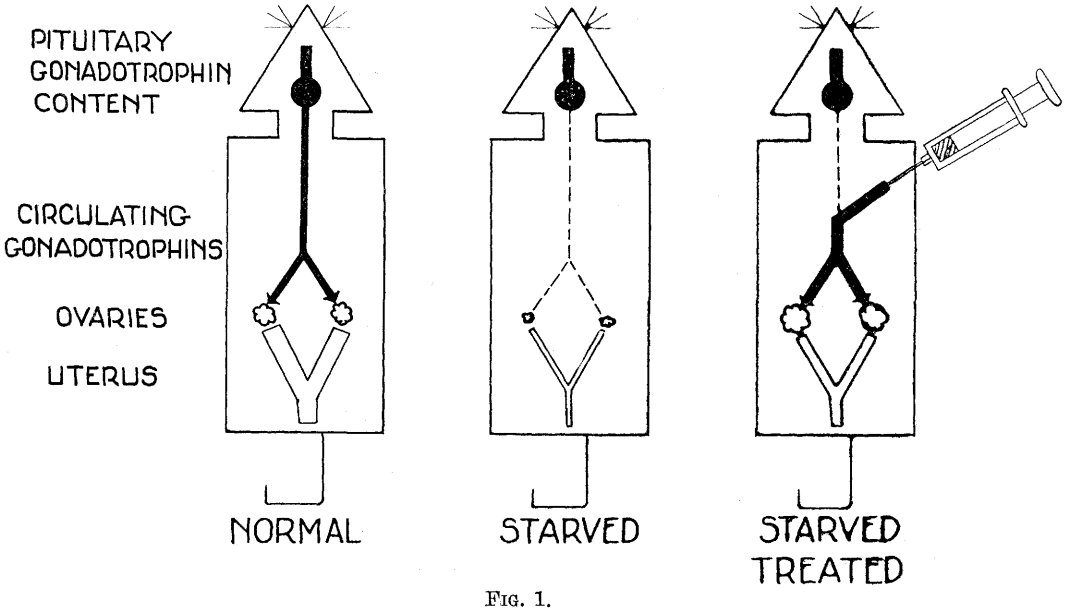

FIG. 1.

anterior pituitary twice a day for 3 days (from the 9th through the 11th day of starvation). A second series of rats (8 months old) were starved for 16 days and compared with fed controls.

Pituitary gonadotrophin content was measured by suspending each anterior pituitary gland in 6.0 cc of water by repeatedly drawing into and expelling from a syringe, then injecting into one 22- to 25-day-old Sprague-Dawley female rat, 1.0 cc twice daily for 3 days. The assay rats were killed 24 hours after the last injection.

Gonadotrophic hormone for injection into the starved adult rats was obtained from the anterior pituitary glands of adult rats castrated 10 months previously. The anterior pituitary glands were suspended in sufficient water so that injecting 0.5 cc twice daily for 3 days equalled administering one half gland.

Results are tabulated in Table I and represented schematically in Fig. 1.

Discussion. The starved rats reacted as if they had been hypophysectomized in that ovaries, uteri and vaginal epithelium underwent marked atrophy. They did not differ from hypophysectomized rats as concerns their potential capacity to respond to exogenously administered gonadotrophins, since administration of rat pituitary suspension, rich in gonadotrophins, restored ovarian, uterine and vaginal cells to normal. Therefore, the conclusion that the circulating blood was low in gonadotrophin content seems warranted.

Pituitary content of gonadotrophin, measured directly, was not below normal. In fact, judged as potency per milligram of gland tissue, the starved rats' pituitary glands (since anterior pituitary weight had fallen circa 40% during starvation) were more potent than normal.

Thus a clear-cut dichotomy between pituitary content of gonadotrophin (normal amounts) and the amount of circulating gonadotrophins (low levels) has been established.

Pituitary content of gonadotrophin is the resultant of the relationship between the amount *produced* and the amount *released*. In acute starvation it is plain that failure of release occurs, as no peripheral gonadotrophin activity is detectable. Production of gonadotrophins must also be decreased since despite the lack of release, excesses are not accumulated within the gland. It is unlikely that the gonadotrophins would remain unchanged within the hypophysis for the entire experimental period of 12-16 days. It is more likely that the release mechanism fails completely and

early in starvation and that the eventual content reflects minimal production.

The mechanism controlling production and release of gonadotrophic hormone during starvation has not been elucidated. The possibility that the amount of circulating gonadotrophins or estrogens are major factors in controlling pituitary content during starvation seems unlikely since gonadotrophin content remains approximately the same despite wide variations in the amount of circulating estrogens and gonadotrophins (high in gonadotrophin injected starved rats, low in starved rats and normal in normal rats).

As a general proposition, release, circulating amount and excretion of gonadotrophins tend to parallel each other. For example, following castration, pituitary content, amount in the circulation and amount in the urine are decidedly greater than for intact animals for all species tested. Following administration of large (unphysiological) amounts of steroid sex hormones to either castrates or normal animals, pituitary content, amount in the circulation and urinary excretion of gonadotrophins fall below normal. Investigation of the 13-lined ground squirrel has revealed that during the period of sexual inactivity (hibernation) gonadal atrophy is associated with decreased amounts of gonadotrophic hormones in the pituitary and in the circulating blood. Just preceding and during the period of sexual activity, there are increased amounts of gonadotrophins in the hypophysis and circulation.[11]

Exceptions to this general proposition, other than the dichotomy found in starvation, have been demonstrated. Lauson, Golden and Sevringhaus[12] observed that immature female albino rats just prior to the onset of puberty had high pituitary levels of gonadotrophins before more than negligible amounts appeared in the circulation. At puberty, release was affected, and with diminishing content, increasing circulating amounts were noted.

Summary. During starvation circulating gonadotrophins fall precipitously whereas the content of hypophyseal gonadotrophin remains as high as under normal circumstances. This is in direct contrast to the usual situation in which pituitary gonadotrophin content accurately reflects the amount released into the circulation.

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In vitro Development of Temporary Penicillin Resistance in Streptococcus Pyogenes.

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The treatment of bacterial infections with penicillin rarely leads to an increase in the resistance of the causative organisms to the antibiotic agent during the course of therapy. While such a phenomenon has been described for *Staph. aureus* and *Strep. viridans*, there is no substantiated evidence that it occurs with *Strep. pyogenes, D. pneumoniae, N. gonorrheae* or other organisms *in vivo*. *In vitro* studies, however, have shown that bacteria may be made less sensitive to penicillin by certain cultural manipulations. Thus, strains of *Staph. aureus*, which were originally susceptible to relatively small doses of penicillin, have been made quite resistant by repeated

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