interspersed with illustrations, charts of distribution and tables with statistical data, all in the place where they rightly belong, that the meaning in most cases is quite evident. Nevertheless, it is a book which deserves to be translated into English. It takes its place next to Murray and Hjort's "The Depths of the Ocean" as one of the indispensable classics.

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SPECIAL ARTICLES

BLOOD CALCIUM IN RELATION TO ANTERIOR PITUITARY AND SEX HORMONES[1]

I

IN this study initial effort was directed to an examination of the evidence for the production by the anterior pituitary (A.P.) of a special "parathyrotropic" hormone—a hormone alleged to stimulate the parathyroids to an increased production of parathormone, which in turn is known to augment the calcium of the blood. As a contribution to this problem it was found that another, and earlier recognized, A.P. hormone is capable of increasing the serum calcium. Later, when it was further found that certain sex hormones induce marked augmentation of the serum calcium in normal, castrate, hypophysectomized or thyroidectomized animals of both sexes, equal or greater interest attached to a development of this aspect of the subject.

II

Since the existence of an A.P. "parathyrotropic" hormone is in question it was essential to examine the serum calcium-raising capacity of those A.P. hormones whose actual existence is not in question. Though this examination could not be made entirely complete the chief result, as obtained on individuals injected for six or more days, were as follows: Prolactin has no power to raise the serum calcium of normal, castrate, hypophysectomized or thyroidectomized pigeons (20 tests, 9.9 mgm per 100 cc: 10.1 mgm control) in either the fasting or non-fasting condition, nor in similar fasting rats (21 tests; 10.2 mgm; 10.1 mgm); prolactin can *decrease* this calcium (even in a shorter period than is considered here) in laying female birds. Cortin, liberated by adrenals—perhaps under the influence of prolactin—is similarly without power to increase the calcium level of such fasting pigeons (23 tests; 9.3 mgm: 9.2 mgm) and hypophysectomized rats (4 tests, 10.2 mgm: 10.0 mgm). A unique Antuitrin G preparation of the growth hormone was wholly without effect on the calcium level of three hypophysectomized pigeons; this particular preparation was shown by our assays to contain much prolactin and some thyrotropic, but to be practically free of follicle-stimulating hormone (F.S.H.). The thyrotropic hormone can not be separately tested, since such preparations invariably have been found admixed with F.S.H. Mixtures of these two hormones gave an increase of 7 per cent. (21 tests); but gonad-stimulating hormone free from thyrotropic—as found in mare serum—gave an average increase of 16 per cent. in similar hypophysectomized pigeons (14 tests) when not fasted. Larger increases are shown by normal adult females.

These results indicate that the long-recognized gonad-stimulating hormone is able—after rather prolonged and adequate dosage—to augment the blood calcium of pigeons. Before a different or a special "parathyrotropic" hormone (based on capacity to increase the calcium of the blood) can be recognized as an entity it is therefore obligatory to exclude either the presence or at least the action (indirect or secondary) of the gonad-stimulator (on sex hormone production; see below). If a second gonad-stimulating hormone, *i.e.*, a "luteinizing" hormone alone capable of stimulating sex hormone production, actually exists —and if mare serum and our own F.S.H.+ preparations from A.P. tissue all contain it—we have no evidence that would select the one or the other of those gonadotropes as the agent mobilizing calcium in these cases. We do not now know whether this gonad stimulator acts independently of, or through, the parathyroids. The possibility remains that the pituitary gland possesses another factor, or a combination of factors, which (through the parathyroids and like parathormone) augments the serum calcium more quickly than does gonadotropic hormone.

Previous work presents a confused picture. Dixon[2] injected rats with an A.P. extract (method not given) sufficient to luteinize their ovaries, found no effect on the serum calcium and suggested the gonad-stimulating hormone is not the one concerned with calcium metabolism.

III

The work of Riddle and Reinhart[3] first showed that the cyclic activity of the ovary is closely concurrent with a very great increase in the serum calcium. Their work, done on pigeons—still the animal superbly suited to this study—was later extended by many investigators to fowl, fish and toads; but in none of that work was it possible to conclude or show that the increase

[1] Aided by a grant from the Carnegie Corporation of New York. Preliminary report.

[2] F. F. Dixon, *Biochem. Jour.*, 27: 410, 1933.

[3] O. Riddle and W. H. Reinhart, *Amer. Jour. Physiol.*, 76: 660, 1926.

TABLE 1
ACTION OF VARIOUS SEX HORMONES ON SERUM CALCIUM

Sex hormone used	Animals used		Dosage		Calcium found per 100 cc serum	
	Kind	No.	Daily	No. of days	Control	Test
			r. u.		mgm	mgm
Theelin (Amniotin)	Normal ♀ doves	2	800	1	10.2	10.7
" "	Normal ♂ ♀ doves	3	40	5	10.5	12.7
" (Progynon)	Hypophysectomized ♂ pigeons	3	200	7	9.4	22.3
" "	Hypct.-castrate ♂ pigeons	2	200	7	9.0	25.1
" "	Hypct.-castrate ♂ rats	2	200	7	9.6	11.1
" "	Thyroidect.-castrate ♂ rats	3	200	7	8.9	11.4
" "	Castrate ♀ rats	2	200	14	10.0	13.1
" "	Normal dogs ♂ ♀	2	300	5	10.3	12.4
Dihydrotheelin benzoate	Hypct.-castrate ♂ pigeons	2	200	7	9.0	14.9
" (Progynon-B) "	Normal ♂ ♀ pigeons	6	200	7	10.0	14.0
" "	Castrate ♀ rats	2	200	7	10.0	10.8
Dihydrotheelin	Hypophysectomized ♂ ♀ pigeons	3	200	6	9.4	10.6
"	Castrate ♂ ♀ rats	3	375	7	10.1	10.9
Theelol (in oil)	Castrate ♂ pigeons	2	100	7	9.6	11.6
" " "	Thyroidect.-castrate rats	2	100	7	8.9	9.0
" (in H_2O)	Castrate ♂ ♀ rats	2	400	5	10.1	10.9
Progesterone	Hypophysectomized pigeons	2	1 mg	6	9.5	10.5
"	Normal ♀ rats	2	0.1 Rb. U.	10	10.7	11.6
Androstenediol	Normal adolescent pigeons	3	3.5 C. U.	7	9.8	9.8
"	Hypophysectomized pigeons	2	3.5 C. U.	7	9.3	9.3
Testosterone	Hypophysectomized ♂ pigeons	2	30 B. U.	7	9.4	9.4
Testosterone oxime	Normal ♂ ♀ pigeons	4	2 mg	7	10.1	9.9
" "	Normal ♂ ♀ rats	2	2 mg	7	10.4	10.0

of calcium was caused by the ovarian hormones which concurrently flood the body fluids of these females. Shapiro and Zwarenstein[4] obtained important data on the toad (*Xenopus*). They conclude, "It is suggested that there is evidence that the principles exerting a hormone-like action on calcium metabolism are not, in the case of the ovary, either oestrin or the luteal hormone, or in the case of the pituitary the gonadotropic hormone." Saviano[5] distinctly increased the serum calcium level in two normal dogs with theelin (progynon), and some of the various clinical applications of this hormone have indicated a like result; but both experimental and clinical results are in a confused state (review by Zwarenstein[6]).

Representative parts of our data on effects of administration of sex hormones on serum calcium, in animals fasted 20 to 24 hours, are given in Table 1. Positive results were obtained with the several species studied (doves, pigeons, fowl, rats, dogs), rabbits excepted.

With dosage prolonged to 6 or 7 days theelin is shown to have high capacity to raise the serum calcium; dihydrotheelinbenzoate ranks next in effectiveness; dihydrotheelin and theelol, in comparable dosage, have a still weaker action which is definitely positive in pigeons but not in rats. Huge doses of corpus luteum hormone (progesterone) have a slight but positive action. Twenty-five capon units of androstenediol —which otherwise shows some actions of both male and female sex hormones—was wholly devoid of calcium-raising action, even in the highly sensitive pigeon. Huge doses of testosterone, and of its oxime, are likewise wholly devoid of such action in both pigeons and rats. Though some forms of the female sex hormone are nearly or quite inert it is thus shown that the common forms of the male and female sex hormones contrast sharply and definitely in their action on cal cium metabolism. We therefore now seem to have the clue to the physiological basis of a prevalent and challenging difference that has long been known to exist—namely, that the sexes differ markedly in their disposition and metabolism of calcium. This difference now appears to rest upon the circumstance that, quite automatically, females produce sex hormones which mobilize calcium (presumably from the bones; this still under study), while the sex hormones predominantly produced by males are without this action.

IV

The extent to which this disclosure assists in clarifying phenomena observed in animals and man is an intriguing, if speculative, subject. Some probable applications in physiology are evident. In medicine it should provide a somewhat surer approach to certain abnormal female states, and possibly disclose the true basis for the benefit currently derived from theelin administration in some mental cases. To students of sex difference it certainly assists a comprehension of the skeletal and mineral metabolism differences which were quite inexplicable so long as the "asexual" thyro-para-

[4] H. A. Shapiro and H. Zwarenstein, *Jour. Exper. Biol.*, 11: 267, 1934.

[5] M. Saviano, *Mem. R. Acad. Naz. Lin., Sci. Fis.*, 6: 165, 1935.

[6] H. Zwarenstein, *Biol. Reviews*, 9: 299, 1934.

thyroid apparatus and vitamin D (this latter being chemically related to the sex hormones) were the prime supervisors of the utilization and deposit of lime. Remembering the more prolonged epiphyseal growth of the bones in human castrates the anatomist and anthropologist may also give consideration to the circumstance that all the several sex cycles of females probably involve temporary interruption of calcium deposit (actual extraction?) in the bones, and perhaps thus account for a lower stature in sister than in brother; and again, they may unite this and a further fact—namely, that in some individuals and races these sex cycles begin earlier than in others—to assist, even if slightly, our understanding of the complicated problem of the statural differences of individuals and races.

V

Summary: Adequate and sufficiently prolonged administration of gonad-stimulating hormone (F.S.H. or perhaps the luteinizer) of the anterior pituitary results in an increase of serum calcium in normal, hypophysectomized or thyroidectomized pigeons; but not in castrates. This action is apparently exerted on tissues producing sex hormone or chemically related substance; the parathyroids may or may not be essential to the response. This action is obtained more quickly in females with intact ovaries than in males or in operated animals of either sex. Prolactin, cortin, F.S.H.-free "growth hormone" and probably thyrotropic do not have this action on blood calcium.

Sufficient and prolonged dosage of certain female sex hormones have great power (theelin), others notably less power (dihydrotheelin, theelol, progesterone), to increase the serum calcium in normal, castrate, hypophysectomized, thyroidectomized pigeons and rats, and in normal doves, fowl and dogs (not obtained in rabbits). Androstenediol and the male sex hormones testosterone and its oxime have no similar or demonstrable power to increase the level of calcium of the blood in these animals.

Some significant applications of the fact that male and female sex hormones contrast sharply in their action on calcium metabolism of normal and suitably operated animals are noted.

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A FIELD CONDITION RESEMBLING NUTRITIONAL ENCEPHALOMALACIA IN CHICKS

IN the course of vitamin E experiments in fowls fed a simplified but otherwise complete diet, Pappenheimer and Goettsch[1] observed a cerebellar disorder in chicks which was apparently of nutritional origin and which was characterized by ataxia and spasms, and histologically by ischemic necrosis in the affected areas. Further studies published in a series of papers culminated in the discovery by Goettsch and Pappenheimer[2] of a hitherto unrecognized protective factor against the experimental disease in certain vegetable oils.

A corresponding disorder has apparently not been recognized in the field. It is the purpose of this communication to record the occurrence of a brain disorder in chicks fed commercial rations which is indistinguishable in symptoms and in gross and histopathology from induced nutritional encephalomalacia.

The first definitely recognized case came to the writer's attention in September, 1935, in a lot of 1,200 Barred Rock chicks four weeks old which had shown symptoms of stupor during the preceding two weeks, with a mortality of 25 per cent. Recovery followed a change in feed. Since that time the disorder has been recognized in 40 specimen consignments comprising 175 chicks, 103 of which represented uncomplicated cases, 16 complicated by affections with *Eimeria tenella,* intestinal coccidiosis, non-specific ingluvitis or *Tetrameres americana;* 56 were histologically negative cases. The specimens came from an affected chick population of 49,800 having an average morbidity of 22.2 per cent. and mortality of 10.6 per cent., the mortality ranging from 0.1 to 42.8 per cent. Hearsay reports on the occurrence of this condition have also come from surrounding New England states. The disturbance was seen most frequently in Barred Rock chicks, probably due to the preference for this variety on the broiler market; it was observed also in Rhode Island and New Hampshire Reds and in White Leghorns. Comparatively large and fast-growing chicks between the ages of 14 and 59 days (average 32.5) appear to be the victims. As far as our records show, two well-known brands of feed were involved, the one 10, and the other 8 times; also home-mixed New England Conference rations, 9 times, and 8 other brands once each, making a total of 11 different feeds.

The symptoms varied from those of droopiness, as seen in the first case, to evidence of muscular incoordination, resting on the pelvic bones with a tendency to fall backwards, retraction of head, somersaults and rotation in a lateral prone position. Coarse tremor was observed occasionally in the legs. The condition was afebrile and ordinarily of rapid onset.

On gross and microscopic study of uncomplicated cases, no abnormalities could be detected in the liver,

[1] A. M. Pappenheimer and M. Goettsch, *Jour. Exp. Med.*, 53: 11, 1931.

[2] M. Goettsch and A. M. Pappenheimer, *Jour. Biol. Chem.*, 114: 673, 1936.