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SUPRARENAL "VIRILISM" IN A DOMESTIC HEN, ITS POSSIBLE SIGNIFICANCE

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THE great majority of hermaphrodites or sex reversals, hitherto described in domestic fowls, have been in old hens and have usually been associated with disease of the ovary and neoformation of testicular tissue. The present case differs essentially in several respects.

It occurred in a Rhode Island Red pullet[1] hatched in December 1934. The group to which it belonged began to lay in June 1935, and evidence will be later submitted favouring the view that this fowl was no exception, although, as trapnesting was not employed, of this there is no conclusive proof. In August 1935, it was noticed for the first time that this pullet differed very markedly from its group members by the possession of a very large, upright, "cocky" comb and wattles. This appearance still persisted in the beginning of September, the "cocky" head furnishings being very much in evidence. The configuration of the body and the colour of the plumage were typically "henny" and spurs were absent. It had never been known to crow and it took no special interest in the other hens. Owing to its age, it was unlikely that it had moulted. No eggs were laid between September 1st and October 7th, on which date it was killed.

Post-mortem examination showed that it was in a very healthy condition, with the ordinary bodily organs and tissues sound. In regard to the sexual organs, the ovary, though small, was not virgin, and, in all probability, the bird had been laying for some time prior to coming under observation. The body of the ovary had a coarse warty appearance, due to its surface being covered with small globular bodies of the size of turnip seed. These were solid and pedunculated and, on microscopic examination later, were found to consist of altered ovarian follicles. At the posterior end of the ovary, there was a pedunculated, round, solid, circumscribed tumour, of the size of a hazel nut, which passed forward anteriorly into a solid tongue of tissue, this extension being surrounded, on all sides, by a mass of cysts containing a clear jelly-like fluid. There was no evidence of growth of any kind from the site of the right gonad, nor was there any macroscopic appearance of the formation of testicular tissue, there or elsewhere. The suprarenals, to the naked eye, appeared normal in colour and shape, but the left was twice as large in diameter as the right. It is to be noted that there was no irregularity in outline of the left gland, such as might occur in a localised tumour formation.

[1] Obtained from Miss B. Findlay, N.D.D., Craibstone, Aberdeen.

The oviduct was fully developed, with a well-formed and complete egg-shell gland. At the time of examination, these organs were in a quiescent, resting condition, but their state of development may be accepted as further evidence that the fowl had laid.

The main part of the tumour, already referred to, was found to consist of macrophages, debris and degenerated remnants of ovarian follicles. The anterior projection was of similar structure, showing in addition, however, large follicles in a state of cystic degeneration. The smaller tumours, which gave rise to the warty appearance of the body of the ovary, consisted of similar but smaller cystically degenerated follicles. No testicular tissue was found anywhere.

The right suprarenal gland showed a normal appearance of islets of cortical tissue, surrounding a central arteriole and being surrounded in turn, in an irregular fashion, by patches of medullary tissue—the whole set in a background of sinusoidal blood vessels. The left gland, however, presented a very different appearance, consisting, as it did, of a network of small groups of cortical cells with less than normal lipoid content, separated from each other by over-abundant sinusoids. The appearance did not suggest mere hyperplasia but was more of the nature of a simple tumour formation, without evidence of malignancy.

It is generally recognised that, in the fowl, the hormone elaborated in the ovary is able to transform the plumage of the neutral bird into the "henny" pattern: and that the testicular hormone has no corresponding effect, a result to be expected since male plumage is practically identical with the neutral variety. There is a belief widely held that the identity of the plumage of the male fowl with that of the neutral bird indicates a genic origin of the neutral plumage (*vide* Danforth in Allen, 1932, p. 38). The fact of this (fortunate) occurrence would seem, however, rather to suggest that, in this particular species of bird, both plumage types are due to the male hormone, and in this possibility lies the interest of such cases as the present one. It would seem to indicate that the male hormone can be produced elsewhere than in the testis, since no testicular tissue was discovered here: and further, that the suprarenal cortex may play a definite role in its formation, a point which will be more fully discussed later. What transpired in this case would seem also to demonstrate the essential antagonism between the ovarian and testicular hormones, in that while the ovarian hormone, produced by the altered but still functioning ovary, is present in amount sufficient to dominate the feathering and body configuration,[1] the male hormone (? produced in the suprarenal cortex) is there also in amount sufficient to sway head furnishings to the male side, a result dependent, in all probability, on a competition between the two factors. The existence of natural hermaphrodites and sex reversals and the results obtained in ovary and testis grafting in birds of the opposite sex show, however, that there is no antagonism in the case of simultaneous existence of the gonads, themselves, in one individual.

It has already been tentatively suggested, from the evidence obtained, that male hormone must be in process of production (in the absence of discoverable testicular

[1] A statement, qualified by the possibility that the fowl was already adult before the tumour developed and that moulting had not taken place since its origination.

tissue) somewhere in the body of this case, and consideration will now be directed more particularly to this point. It is appropriate to mention, in the first place, in this connection that Lipschütz (1924) has on record a case described by Berner, which appears to resemble closely the present one. The general history of the bird, except for the fact that it had spurs and had never laid, is the same. Most important, however, is the fact that in it there was found a tumour of the suprarenal gland, to which is attributed the abnormalities existent. The striking similarity of this case (the only one, so far as one can find, previously recorded) to the present one, with a common lesion in the suprarenal cortex, goes far to suggest that the suprarenal cortex, in both, is the site of formation of the male hormone and that, in both, the tumour development was the primary cause of the *symptôme complex* which later developed.

Such a theory is supported by the facts as they exist in regard to the occurrence of "virilism" in women, a condition likewise associated with tumours of the suprarenal cortex which need not be dealt with at length here. One need only mention, in this regard, that Glynn & Hewetson (1913) found that adrenal cortical "rests" or bilateral hyperplasia of the adrenal cortex was to be noted in 15 per cent. of female, but only in 0·7 per cent. of male, pseudohermaphrodites. Broster & Vines (1933) discuss at length the question of "virilism" in human beings as being due to hyperplasias of the suprarenal cortex and direct attention to the presence of a characteristic fuchsinophile substance in the cells of the cortex in such cases. Zawadowsky's observations on castrated hens, without subsequent development of right rudimentary gonad into a testis (*vide* Lipschütz, p. 312) and where comb, wattles and sexual activity of the male appeared, may also be interpreted in the same sense. The facts elicited by Riddle (1925) in his gonadless pigeons (produced by wide crossings), where male sexual behaviour appeared in all his hybrids, is capable of explanation on a similar basis. Lespinasse (1922), too, records the occurrence of precocious male sexual behaviour in young cocks, into the breast muscles of which had been engrafted suprarenal glands. If the suprarenal has indeed, as suggested, the capacity of producing the male hormone, the question arises as to how it acquired this power. In previous papers (McGowan, 1930 *a*, *b*), this subject has been discussed and the theory advanced that the cells of the suprarenal cortex, like the interstitial cells of the ovary and testis, are macrophagic cells of the reticulo-endothelial system, derived, in their first origin, from the ordinary peritoneal epithelium covering the germinal ridge of the embryo. In the case of the suprarenal cortical cells, the ancestral somatic peritoneal cells, after having invaded the underlying tissues of the embryo, would appear to make contact with the medullary cords of the primitive gonad, which contain primitive germ cells[1] (*vide* Lillie, 1919). These latter, male in type in the fowl embryo, are subject to a considerable amount of degenerative changes, even in cases where a testis is eventually formed. In such cir-

[1] Witschi (*vide* Allen, 1932, chap. v) suggests that the cortical zone of the gonad acts as a female, and the medulla as a male inductor. The bearing of this on the present question is obvious. A basis for an explanation of the bisexuality of the soma of vertebrates, other than a genic one, may also be forthcoming if, in this context, the implications of the dominance of maleness and of the origination, before other parts of the ovary and testis, of the primary cortical zone in the ovary (? female inductor) be recognised.

cumstances, it is reasonable to suppose that the *anlage* of the cortex, consisting as it does of somatic peritoneal cells of known phagocytic capacity, in its contact with the medullary cords might phagocyte these degenerating "male" cells (germ cells), absorb their essence and transmit it to its descendants, when it finally settles in its definitive site in the cortex. No greater, indeed a much less, assumption is involved here, to speak of one aspect only, than in that, subscribed to by many investigators, *e.g.* Firket, Gatenby, Brambell, Fell, etc., that the primitive germ cells die out and the definitive germ cells are derived from the descendants of the ordinary somatic peritoneal epithelium, which originally accompanied the primitive germ cells in the sexual cords.[1] There exist, moreover, several circumstances in support of the view advanced here. Krabbe (*vide* Sharpey-Schafer, p. 413) explains the "virilism" in women, above referred to, in a manner which incorporates the basic idea advanced here, by the growth, in the suprarenal cortex, of primitive germ cells (male in type), which had become entangled in the cortical *anlage* when it made contact with the medullary cords of the primitive gonad. Elliot & Armour (1911) mention the occurrence of cortical "rests" in the testis and in the broad ligament of the female (but not in the ovary itself), points, when anatomically considered, of significance in relation to the fate of the medullary cords and their association with the cortical *anlage*.

It has been indicated that the cells of the suprarenal cortex are considered to be somatic cells, belonging essentially to the reticulo-endothelial system, and a few additional remarks may be made on this subject. Glynn (Glynn & Hewetson, 1913) is emphatic that the cortical tissues, in spite of their superficial epithelial appearance, are in reality mesoblastic in origin and that the tumours derived from them are, not epitheliomata, but sarcomata. Their special relationship to the reticulo-endothelial system would also appear to be vouched for by the frequent perivascular nature of the tumours arising in the suprarenal cortex (*vide* Ewing, 1922); while the occurrence of histioblasts ("resting wandering cells", "lymphoidocytes"), as a transition stage in the formation of cortical cells (in the area immediately surrounding the arterioles[2] in the centre of the cortical masses of the suprarenal of the fowl in certain types of leucosis (McGowan, 1930 *a*)), points in the same direction, since this region is one of the reservoirs for reticulo-endothelial elements.

Goldschmidt (*vide* Brambell, 1930) has demonstrated that a time factor, in regard to the appearance in the embryo, of the male stimulus, exerts a considerable

[1] There are, however, explanations of the facts, as alleged, which are quite compatible with the continued existence of the primitive germ cells and with Weismann's theory of the continuity of the germ plasm. With regard to the so-called "endocrine hermaphroditism" following a phase of pure maleness in sinistral ovariotomy of the fowl (*vide* Witschi in Allen, 1932, p. 210) the usual explanation of this phenomenon would, it seems, be the negation of all sexual hormone theory. It is here suggested that the ovarian hormone in such cases, in the complete absence of ova, is on a similar footing to the male hormone in the adrenal cortex, being formed in the phagocytic cells and their descendants which have arisen from remnants of the left ovary and possibly also from the cortex of the right gonad.

[2] The relationship of the arterioles to the cortical cells (mesoblastic) and to the sinusoids is the same as that of the hepatic arterioles to the columns of liver cells and to the sinusoids of the liver lobules. Moreover, the basic architecture in these two organs, as also in the spleen and lymphatic gland, would seem to consist essentially of the invagination of arterioles and periarteriolar structures into the lumen of a vein or, in the case of the lymphatic gland, of a lymphatic vessel.

influence in the evolution of the gonads from their primitive undeveloped state. Amongst other things, also, the condition of parthenogenesis would seem to indicate that the earliest formed gonad, phylogenetically speaking, is the ovary; and that later on, as a secondary development, phylogenetically and ontogenetically speaking, maleness, associated with the appearance of a testis, arises. Thereafter, in birds and mammals, the stimulus for development of the testis (which in Amphibia and the lower orders appears later than that for the ovary) overtakes and leaves behind the ovarian one, a point, it would seem, of more than ordinary importance. Thus, in juvenile hermaphroditism of the frog, with development subsequently to the male from a primitive ovarian condition, the time factor of the arrival of the male determining stimulus decides, by the time of its appearance, the point as to whether the embryo in question will be a female (very late), an intersex (not so late), or a male (early).[1] It is interesting to speculate, in these circumstances, whether the suprarenal cortex in the frog (in view of ovarian tissue alone being in existence at the time the cortical *anlage* makes its contact) will have a feminising influence on the soma. One may contrast with this hypothetical state of affairs, the existence of the very definite masculinising influence of the cortex in birds and mammals, where the contact is made, in this case, with testicular tissue. This arises from the fact that the male-determining stimulus, in its time of arrival, has been so speeded up that testicular tissue is already developed (in the medullary portion of the primitive gonad) considerably in advance of the ovarian (in the cortical region of the gonad, which ultimately becomes an ovary). This speculation could be pursued still further backwards, phylogenetically speaking, and inquiry made as to what tissue, if any, plays the part of the suprarenal cortex in orders lower still where cortical tissue, as such, is not known to exist.

As regards the essential function of the suprarenal cortex, if regard be had to the part played by the gonads in modifying and transforming the soma in the direction of elaborating the accessory sex characters, etc., it seems likely that the suprarenal cortex (in collaboration, of course, with the genes and gradient fields) may have an influence in moulding the neutral soma and in making it conform to the configuration, etc., represented by the primitive germ cells. The ever increasing close association of the cortical tissue with the vegetative nervous system, as represented by the suprarenal medulla, is significant in this connection. The function of the cortex in the adult, however, may quite well be very different from that fulfilled by it in various stages of phylogeny and ontogeny, especially in view of the fact that the tumour cells in the present case tend to the embryonic, in a manner paralleled by several other bodily organs in their development, *e.g.* some of accessory sexual organs, pineal body, thyroid, thymus, etc.

A word may be said in conclusion as to how the suprarenal cortex (and the gonads) may possibly bring about the modification of the soma. The simile of the anterior pituitary acting as a leader in the orchestra of the endocrine organs is well

[1] Goldschmidt's view is also of great interest in connection with Witschi's (*vide supra*) theory regarding cortical and medullary inductors and the problem of the bisexual soma in vertebrates. In view of it too the speculation which occurs in the next sentence may be superfluous in that the medulla, as such and without the arrival of gonadal tissue, may be capable of male induction.

known. This musical simile may be carried a stage further by comparing the reaction of the soma to the subordinate endocrine organs, etc., to that of music produced by a pianola. The genes of the somatic cells, alike in every cell in the body, may be compared to the air (under pressure) in the air vents. A note (or a tune) can be produced only when a perforation on the roll (a highly intricate and specific regulator) comes opposite an air port. The blood and nervous supply together with the local environment and the relative hormone resemble the perforations in that they release the potential of the genes and thus originate specific growth and adaptation for function.

SUMMARY

A case of suprarenal "virilism" in the hen, due to a tumour of suprarenal cortical tissue, has been described and the possible bearing of this occurrence on the origin, structure and function of the suprarenal cortex discussed.

REFERENCES

ALLEN, E. (1932). *Sex and Internal Secretions.* Baltimore.

BRAMBELL, F. W. R. (1930). *The Development of Sex in Vertebrates.* London.

BROSTER, L. R. & VINES, H. W. C. (1933). *The Adrenal Cortex: A Surgical and Pathological Study.* London: Lewis.

BERNER, O. *Vide* Lipschütz, p. 393.

ELLIOT, T. R. & ARMOUR, R. G. (1911). *J. Path. Bact.* **15**, 481.

EWING, J. (1922). *Neoplastic Diseases*, pp. 770, 759.

GLYNN, E. E. & HEWETSON, J. T. (1913). *J. Path. Bact.* **18**, 81.

GOLDSCHMIDT, R. *Vide* Brambell, p. 164.

KRABBE, K. H. *Vide* Sharpey-Schafer, p. 413.

LESPINASSE (1922). Barker's *Endocrinology and Metabolism*, **2**, 511.

LILLIE, F. R. (1919). *The Development of the Chick*, p. 403. New York.

LIPSCHÜTZ, A. (1924). *The Internal Secretions of the Sex Glands* (edited by Marshall). Cambridge.

McGOWAN, J. P. (1930 *a*). *Edinb. med. J.* **37**, 545.

McGOWAN, J. P. (1930 *b*). *J. Cancer Res.* **14**, No. 4.

RIDDLE, O. (1925). *Brit. J. exp. Biol.* **2**, 211.

SHARPEY-SCHAFER, E. S. (1924). *Endocrine Organs*, **1**.

ZAWADOWSKY, M. (1922). *Das Geschlecht und die Entwickelung der Geschlechtswerkmale.* Moscow.