function of each retina is slowly destroyed, whether the process begins diffusely or first attacks one special region, as the juxtapapillary zone or the macula. The final outcome, if the patient survives long enough, is complete atrophic pallor throughout the fundi—a condition sometimes misinterpreted as congenital choroideremia. Choroidal haemorrhages are more rapidly destructive than sclerosis, but the two are not mutually exclusive; they can occur side by side in high myopia and in Dooyne's "honeycomb" familial choroiditis. Finally, another latent source of retinal anoxia should be borne in mind to account for defective vision, and that is atheromatous change in the central retinal artery immediately behind the optic disk, outside the range of the ophthalmoscope.

General Conclusions and Summary

In proportion to its size the ocular fundus has perhaps been more minutely surveyed than any part of the human frame, not even excepting the lens and cornea. Repeated ophthalmoscopic observations fortified by histological study and correlated with the rest of the clinical background make a foundation upon which the prognosis may be built. Complete certainty is seldom attainable, but marshalling of all the evidence does at least permit an approximate forecast. Although prognosis must be to a large extent based upon work done in the past, it is nevertheless essential to link up the facts with recent advances. New methods of therapy together with changing aetiological situations have within living memory altered the outlook in many important diseases, notably hyperpiesis and diabetes. The state of the fundus vessels will probably for a long time continue to be one of the more important considerations for all who seek to assess the cardiovascular system.

Changes in the ophthalmoscopic appearances of vessels in the fundus may supply guidance about the future prospects of (a) one eye, (b) both eyes, and (c) the other organs and tissues of the body. Thus it is possible to say, when confronted with a typical instance of Coats's disease, that the affected eye is likely to deteriorate, but the second eye will probably escape. In Eales's disease, on the other hand, the chances are that the fellow-eye will be implicated, even if it betrays no pathological signs long after the disease has become manifest in the first eye. Characteristic alterations in the fundus vessels may also be evident in hyperpiesia, hyperpiesis secondary to non-cardiovascular disease, diabetes, haematopoietic maladies, and many other abnormal states.

The prognostic implications of retinal vascular phenomena are not always self-evident. Legitimate conclusions from them can only be achieved by careful weighing of the ophthalmic and systemic evidence. The role of spasm in the production of arteriosclerotic retinopathy is not yet settled, but it does seem probable that spasm has been too readily assumed as an explanation for events that are probably due to obliterative changes in the vessel walls.

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RECENT RESEARCH IN PHYSIOLOGY OF BREAST APPLIED TO MAMMARY CANCER

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It may be salutary to doubt but it is impossible to deny that approximately 50% of human breast cancers are hormone-dependent and do not possess the gloomy and mysterious attribute of "autonomy" so often regarded as the essential biological characteristic of all malignant tumours. A breast cancer is said to be hormone-dependent if progressive proliferation of its infiltrating and metastasizing cells is conditioned by an adequate supply of the specific mammatrophic hormones which are responsible for physiological mammogenesis whereby the mammary rudiments of the weanling reach the structural complexity of sexual maturity and the functional maturity of lactation. It is clear, therefore, that our control of hormone-dependent breast cancer primarily depends on our knowledge of mammary physiology.

Hormonal Control of the Normal Breast

Five years ago it was generally believed that the proliferation of the hormone-dependent epithelium of the normal

female breast was controlled by steroid hormones produced by the ovaries and that pituitary hormones, although sharing this responsibility to a minor degree, were mainly concerned with lactation. Since then the pituitary has been increasingly implicated in the process of normal mammatogenesis. A. T. Cowie and J. S. Folley (of the National Institute for Research in Dairying, Reading) have reviewed the large volume of recently acquired experimental evidence which clearly identifies pituitary prolactin as the key hormone primarily responsible for normal mammary growth. The work of Lyons, Li, and their collaborators, carried out in the Department of Anatomy and the Hormone Research Laboratory of the University of California, has provided most of this recent evidence derived from experiments in which they used weanling male rats aged about 26 days. At this age, although rudimentary, the mammary glands have already started to grow slowly and the main ducts have short branches, only a few of which carry terminal clubs. In spite of their simple structure these mammary rudiments are remarkably reactive to appropriate hormonal stimuli and in a few days can be rapidly "feminized" and even induced to lactate; these responses are striking and easy to recognize.

Groups of these animals were gonadectomized and hypophysectomized. The inevitable result of this radical endocrine ablation was to produce rapid and striking atrophy in the slowly growing mammary rudiments, and it is highly significant that the administration of ovarian steroid hormones in any combination and over a wide dose range was completely powerless to arrest this atrophic process. The response to prolactin was equally significant. The mammary atrophy was delayed but the glands showed no evidence of a progressive growth response. On the other hand, a spectacular response was readily and rapidly obtained when prolactin and ovarian hormones were injected together. This combination of a protein hormone of pituitary origin with steroid hormones of ovarian origin was able, in 14 days, to induce a sufficiently powerful mammary growth response to raise the structural status of these male mammary glands to that found at mid-pregnancy in the female. This effect was obtained when a relatively large amount of prolactin was given with a surprisingly small amount of oestrone, and if pituitary growth hormone was added to this combination the glands reached the status of pregnancy at full term. If the animal was brought to a more physiological condition by giving growth hormone and cortisone in addition to prolactin and oestrone, the rapidly growing mammary glands of these weanling males could be induced to lactate. It is highly significant that *when prolactin was omitted from any of these hormone combinations it was quite impossible to produce anything more than a strictly limited degree of duct proliferation.*

These experiments are the latest in a long research programme which supplied the factual data and experimental experience upon which they were planned. They implicate prolactin to a high degree of probability as the primary pituitary factor concerned in maintaining mammary growth in all its phases, and demonstrate that this depends upon a finely balanced synergistic mechanism which stimulates the growth of the mammary gland when prolactin is at a relatively high concentration and oestrogen at a surprisingly low one.

The optimal growth responses were obtained in the hypophysectomized and gonadectomized male rat when 4,000 parts by weight of prolactin (molecular weight 33,000) acted in synergism with 1 part of oestrone (molecular weight 240)—that is, when the relative molecular concentration of prolactin was 30 and that of oestrone was 1.

Mammatrophic Potency of Human Urine

Two trophic hormones, both of which are proteins, can be demonstrated in human urine with comparative ease. Pituitary gonadotrophin is present in relatively large quantities in the urine of approximately 50% of normal post-

menopausal women. Chorionic gonadotrophin is so easily demonstrated in the urine of all pregnant women, and in that of men suffering from certain testicular tumours, that its certain identification in the urine has become a routine procedure in clinical diagnosis.

As long ago as 1934 Lyons and Page showed that the urine of lactating women produces a specific secretory response when injected into the pigeon crop, and Coppedge and Segaloff (1951) and Segaloff *et al.* (1951), again using the pigeon crop, have elaborated a bio-assay technique which they claim measures the prolactin activity of human urine (Segaloff, 1953). It has more recently been demonstrated that the urine of all normal premenopausal women during the second half of the menstrual cycle will rapidly and powerfully stimulate growth and differentiation in the mammary rudiments of weanling male mice (Scowen and Hadfield, 1955; Hadfield and Young, 1956a), and that the urine of 58% of normal post-menopausal women can "feminize" these rudimentary mammary glands in the same way and with equal rapidity (Hadfield and Young, 1956b).

In our experiments untreated human urine was injected into weanling male mice twice daily for five days. Ten mice were used for each experiment, and as each mouse yielded an average of five mammary glands the growth response induced by each urine was judged by studying the intensity of the reaction produced in 50 rudimentary mammary glands. The response has two phases:

1. A growth phase, which rapidly produces an extensive duct system due to the formation of a gross numerical excess of large deeply staining terminal clubs at the growing ends of the ducts (see Fig. 2).
2. A differentiation phase whereby the terminal clubs are transformed into clusters of gland tubules producing easily recognizable primitive breast lobules (see Figs. 3 and 4).

As each "club" is a focus of intense cellular proliferation and consists of a mass of undifferentiated mammary epithelium in which there are many mitoses, the intensity of the response was determined by enumerating the total number of clubs and terminal lobules in all the mammary glands dissected from 10 mice. From this the average number of clubs and terminal lobules per gland was calculated; the result, when corrected for the average number of clubs per normal gland in the weanlings of the strain of mouse used in these experiments, gives a reasonably accurate measure of the intensity of the experimentally induced response. The mammary glands of the normal untreated weanlings in our strain carry 1.14 clubs per gland, and, an average of four or more clubs per gland being statistically significant of recent growth acceleration, we conclude, if 10 injections of urine over five days produce a figure of this order or more, that the urine contains one or probably more than one specific mammatrophic hormone.

The growth response following the injection of premenopausal urine lies at the relatively low level of 5 ± 1 during the first half of the menstrual cycle and rises after the 16th day to reach an average of 12 ± 2 on the 18th day. In a series of urines from 57 normal women at post-menopausal ages ranging from 1 to 30 years, 58% showed a positive growth response varying from 4.5 to 12. In approximately

GEOFFREY HADFIELD: LEGEND FOR ILLUSTRATION

FIGS. 1 to 4.—Whole-gland mounts of mouse mammary showing the reactions to the injection of human urine, to oestrone, and to prolactin. ($\times 7$). Fig. 1: Untreated normal controls showing variation in complexity of mammary in weanling males of the strain used. Fig. 2: The growth response produced by oestrone. Fig. 3: The combined growth and differentiation response produced by prolactin. Fig. 4: The response to human premenopausal urine in the second half of the menstrual cycle. Note the similarity to the prolactin response.

20% the urine produced no response, and in the remainder it was "borderline" (Hadfield and Young, 1956b).*

When oestrone over a wide dose range was injected twice daily for five days an optimal response was induced at a dose of 10 μ g. over five days—that is, 1 μ g. per dose. All glands responded and well-developed duct systems were produced, but it is highly significant that in only 9.5% of the glands was there any evidence that the terminal clubs were "acinized" (see Fig. 2). On the other hand, the injection of a potent urine over the same period was not only followed by an equally vigorous growth of ducts but no less than 38% of the glands showed unmistakable acinization (see Fig. 4). Prolactin produced a vigorous reaction in the weanling male mammae, the optimal dose, 5,000 μ g., being very large compared with that of oestrone, and at this level at least 32% of the mammary glands reacting to prolactin showed well-developed glandular differentiation (see Fig. 3).

From the purely morphological point of view, therefore, the five-day response to the injection of human urine closely resembles that induced by prolactin over the same period and is significantly different from the five-day oestrone response, for this hormone must be injected for eight days at least before a comparable degree of acinization is obtained.

Application to Breast Cancer

Oophorectomy and adrenalectomy temporarily abolish oestrogen production and are usually followed by a growth regression in hormone-dependent breast cancer. It often happens, however, that after a period of months oestrogens, usually in low concentration, again appear in the urine. The tissue of origin of these oestrogens is obscure, but it is possible that the retroperitoneal mesenchyme from which the ovaries and adrenal cortex are developed retains its potentiality to produce oestrogens and may be responsible for their delayed production and slow reappearance in the urine. In a disappointingly large proportion of breast-cancer patients whose ovaries and adrenals have been removed, progressive growth of the tumour and its metastases becomes re-established after a period of growth regression which rarely exceeds two years. It is difficult to escape the conclusion that this phenomenon is due to re-establishment of oestrogen production at a low level, for the Californian experiments have shown that the quantity of oestrogen relative to prolactin required for normal breast growth is small.

On the other hand, it is often and probably too readily assumed when a breast cancer recurs under the above conditions that it has acquired *secondary* hormone independence. This view is not acceptable, in some cases at least, for a second significant regression of growth may be produced by hypophysectomy. It would be safer, therefore, to ascribe this second period of growth acceleration to re-establishment of oestrogen production and to assume that removal of the ovaries and adrenals rarely results in "steroprivation"—that is, total and permanent suppression of oestrogen production—even at the low level required for normal mammarygenesis.

Apart from the surgical and clinical difficulties it entails, hypophysectomy is obviously supported by the recent additions to our knowledge of mammary physiology, for not

only does it cut off the supply of prolactin but it deprives the tissues and target organs capable of producing oestrogen of the appropriate trophic stimulus which leads to its elaboration. To achieve its purpose hypophysectomy must be total. Animal experiments have shown that if as little as 5% of the gland is left behind pituitary function will be restored in a relatively short time. We must therefore regard the cells of the anterior lobe as having considerable powers of regenerative hyperplasia. For this reason simple section of the pituitary stalk is unlikely permanently to abolish pituitary function, since it leaves behind a perfect organ graft having very considerable growth potential which, judging from animal experiments, quickly becomes richly vascularized (Harris and Jacobsohn, 1952), and from clinical experience can establish vascular connexions with the hypothalamus after incomplete surgical removal of the hypophysis.

If hypophysectomy has been total it should produce a precipitate and permanent fall in the mammotrophic and gonadotrophic potencies of the urine to a level which indicates that the production of prolactin and gonadotrophin has ceased, there should be clinically recognizable thyroid deficiency, and signs of adrenal cortical deficiency should appear after cortisone withdrawal.

The disappointing results of failure to remove or destroy the whole hypophysis should not be allowed to cast doubts on the validity of the experimental evidence which supports total hypophysectomy; nor should it be too readily concluded that a tumour has developed secondary independence when a growth regression after hypophysectomy is followed by a period of growth acceleration. Such a conclusion would be unjustifiable if, coinciding with growth acceleration, there was a significant rise in the mammotrophic potency of the urine.

We are probably on safer ground in the case of primary hormone-independent cancer, the reality of which appears to be undoubted. Approximately 50% of human breast cancers fall into this group, and in approximately the same percentage of normal post-menopausal women the urine shows little or no mammotrophic potency. Combined with our more recently acquired knowledge of mammary physiology, this evidence supports the conclusion that a breast-cancer patient who excretes little or no mammotrophic hormones in her urine has a pituitary-independent tumour and that no regression of tumour growth could be expected to follow total removal or destruction of her hypophysis.

It is theoretically possible that pituitary-independent breast cancer may occur, in spite of the fact that the hypophysis is producing prolactin at a normal level. From a limited number of investigations this would appear to be uncommon, and a high pre-operative mammotrophic potency has usually been associated with significant growth regression after hypophysectomy, whilst a low pre-operative mammotrophic potency has been only rarely followed by regression in growth of the tumour and its metastases. The accurate assessment of this relationship demands repeated estimations over a long period on a large number of patients before and after total hypophysectomy. Our observations, although certainly suggestive, are at present too few to make a confident statement. A precipitate fall in the urinary mammotrophic potency during the first few weeks after hypophysectomy has been more frequently observed, and there is some evidence that during this period the urine may become remarkably lethal to weanling mice. This may be due to the presence in the urine of split products derived from autolysing tumour cells. From the observations of Foulds this would appear to be a reasonable suggestion.

This author was the first to describe a naturally occurring, highly typical hormone-dependent breast cancer in mice, arising during pregnancy and rapidly regressing at the time of parturition or soon after. Within a day or two regression is far advanced. The tumour cells show widespread nuclear karyorrhexis and extreme cytoplasmic vacuolation, and in a

*It is possible by extracting the urine to obtain considerably higher values than these, and we have found that if 1% by weight of NaCl and 4 volumes of absolute alcohol are added to a large volume of acidified urine the precipitate obtained carries all the prolactin activity of the specimen. This is, however, firmly bound to the voluminous phosphatic deposit which comes down with all specimens of urine, with the notable exception of those from pregnant women. The introduction of a long extraction into the method detracts from its clinical value, and as specimens of unextracted urine passed immediately after six hours' sleep gives easily recognizable growth responses, we are satisfied that, for clinical purposes at least, any extraction process can be justifiably omitted.

remarkably short time the site of the carcinoma is replaced by avascular scar.

It is generally agreed that prolactin is richly contained in the mammalian placenta, where it may be elaborated or, more probably, stored, and the dramatic growth regression of the Foulds tumour at parturition suggests that it is "placental-prolactin" dependent. Strict hormone dependence is also characteristic of the malignant tumours in animals produced experimentally by hormone administration.

Hormone dependence in mammals may therefore be regarded as an induced or spontaneous biological characteristic whose existence should dispel any doubts regarding the reality of hormone-dependent human breast cancer.

Summary

About 50% of all human breast cancers are hormone-dependent. Progressive growth of such tumours is conditioned by an adequate supply of those hormones which govern physiological growth in the hormone-dependent epithelium of the normal mammary gland.

Normal breast growth is controlled by the synergistic action of the pituitary hormone prolactin acting at a relatively high concentration, with ovarian oestrogen acting at a relatively low one.

Combined oophorectomy and adrenalectomy deprive a breast cancer of oestrogenic steroids, and if the tumour is hormone-dependent growth regression follows. This effect seems to be almost always temporary, oestrogen production is slowly re-established, and progressive growth of the tumour recurs probably when oestrogen production from an unknown site reaches the low level required for normal mammatogenesis.

Total hypophysectomy in all probability completely deprives the tumour of oestrogen and prolactin.

This operation can have no effect on the growth of a hormone-independent tumour.

The urine of all pre-menopausal women and of approximately 50% of post-menopausal women contains one or more mammatrophic hormones. It seems probable that it contains prolactin.

If the urine of a breast-cancer patient has no mammatrophic activity it seems very probable that her tumour would be hormone-independent and that hypophysectomy would have no effect on its progressive growth. A short series of investigations supports this supposition.

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CORTISONE IN TREATMENT OF CHILDREN WITH CHRONIC ASTHMA

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The conflicting reports on the value of corticotrophin (A.C.T.H.) and cortisone in "asthma" relate chiefly to adults and are probably due in part to the ephemeral nature of the disease and in part to the different methods of assessment employed.

In the investigation reported here the main object was to assess the value of oral cortisone in improving the ventilatory function of children with chronic "wheezy" chests. A further object was to compare the effect on the ventilatory function of such children of cortisone given by mouth and adrenaline given by inhalation.

Present Investigation

Children Studied.—Twelve children attending an asthma clinic were selected for study, all of whom had asthma associated with a poor ventilatory function. The children selected had all attended regularly at the clinic for respiratory function tests for not less than six months, and seven had done so for from two to four and a half years. Only those who could attend regularly twice weekly and could co-operate well in the tests were selected. Details of each child are summarized in Table I. There were nine boys and three girls, whose ages ranged from 9 to 15 years. All had been found to have impaired ventilatory function between their acute attacks and also when free from symptoms. The duration of their symptoms ranged from two and a half to twelve years, six children having started their attacks in the first three years of life. When possible, the patients were grouped into two main types—allergic spasmodic asthma and infective asthmatic bronchitis—as judged by their histories, and special notes were made on the psychological background, which varied in importance. Seven cases were of allergic type, and in four of these psychological factors were thought to be of special importance. One case was primarily infective and four cases were of mixed type, having characteristics of both the allergic and the infective groups.

Method of Assessment.—After having observed "asthmatic" children attending the clinic for periods of up to five years we are convinced of the necessity of employing an objective measure for the assessment of therapy. In this investigation we have measured the expiratory flow rate over the first 0.75 second of expiration (E.F.R.⁴⁰) as described by Kennedy (1953). This measure is an index of the maximum ventilatory capacity at a theoretical respiratory rate of 40 breaths a minute (hence E.F.R.⁴⁰), and we consider it to be valid and practicable in the assessment of children with asthma.

Treatment Regime.—As a routine, all children attended the clinic twice weekly, when they were given an inhalation of adrenaline (1/1,000) for a period of