

having been satisfactorily explained, interest was focused on the rising anti-D titre. After repetition of the tests it was concluded that the rise was more than could be accounted for by technical error.

This would therefore appear to be an example of an anamnestic reaction. While others have apparently observed the phenomenon in connexion with Rh agglutinins, only one case has been recorded so far (Davidsohn, 1948). The latter described the case of a woman who had an affected child by a homozygous husband and three years later became pregnant by a D-negative artificial insemination donor. A normal D-negative child was subsequently born, but a marked rise in agglutinins was observed about the sixth month of pregnancy. In the bacteriological field, in which anamnestic reactions have previously been studied, attempts to reproduce the phenomenon experimentally have not given consistent results. However, it has been pointed out (Topley and Wilson, 1936) that where an appreciable rise did occur in response to the introduction of a second antigen, the latter bore some relation to the primary antigen.

Our knowledge of the chemistry of the blood-group antigens has been considerably increased in respect of the ABO system (Morgan, 1947), but is very much more scanty so far as the other antigens are concerned. However, one might reasonably look in this direction for a source of antigenic stimulation in anamnestic reactions, since they apparently occur amongst the ABO substances (Davidsohn, 1948).

In Davidsohn's case there was no ABO incompatibility between the mother and infant, and the MN grouping of the mother was not known. In the present case the only foreign antigen is the M derived from the MN cells of the infant. This is known to be a weak antigen in man, and anti-M has been detected in human serum (Paterson, Race, and Taylor, 1942). Whether M has anything in common with the Rh antigens is a matter for speculation, but the failure to detect anti-M in the mother's serum would seem to rule out any possibility of M being responsible for the rise in anti-D titre in this case.

The problem remains, therefore, in both its clinical and its more academic aspects. From a practical point of view a rising anti-D titre will result in one of three possibilities: (1) an affected D-positive infant, (2) an unaffected D-positive infant, or (3) an unaffected D-negative infant (anamnestic reaction). In coming to a decision the obstetrician will undoubtedly set against induction the second and third possibilities. There are grounds for hoping that in the not too distant future an explanation of why a positive infant may escape can be turned to practical advantage, and in order that the third possibility may be put into its proper perspective it is obviously relevant to know how often an anamnestic reaction may occur.

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CARCINOMA OF THE BREAST IN CASTRATED WOMEN

BY

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Although it well known that carcinoma of the breast may occur after the natural menopause, and although it is also established that women of 60 and 70 may suffer from acute carcinomatous mastitis, carcinoma of the breast occurring after castration, performed either by irradiation or by surgery, is a less familiar condition. At a time when castration is being suggested by many workers as a sound adjuvant in the treatment of cancer it is useful to recall the following facts.

Anatomical and Clinical Data

1. *Frequency*.—In 2,000 cases of carcinoma of the breast I have found 32 (1.6%) occurring in castrated women (statistics from the Centre Anticancéreux, Lyons). This figure is higher than that of carcinoma occurring during pregnancy (21, or 1.05%) or in men (16, or 0.8%).

Summary of Results

Case No.	Castration			Age at Onset of Carcinoma	Age at Death	Remarks
	Reason	Means	Age			
1	Fibroids	X rays	28	43	49	
2	"	Surgery	32	35	36	
3	"	X rays	32	53	54	
4	Miscellaneous	Surgery	36	37	43	
5	Fibroids	"	37	41	42	
6	Miscellaneous	"	37	51	56	
7	Fibroids	X rays	38	45	57	
8	"	Surgery	39	46	47	
9	"	"	40	63		Alive aged 85. No recurrence
10	Miscellaneous	"	40	64		Alive aged 67. No recurrence
11	"	"	41	58	62	
12	Carcinoma of cervix	"	42	49	52	
13	Double pyosalpinx	"	42	50	51	
14	Fibroids	"	42	55	58	
15	"	"	42	62		Alive aged 80. No recurrence
16	"	"	43	44		Alive aged 65. No recurrence
17	"	Radium	43	53	57	
18	Ovarian tumour	Surgery	43	57		Alive aged 62. Recurrence
19	Fibroids	"	44	64	66	
20	Metropathia	X rays	45	47	57	
21	Fibroids	Surgery	45	51		Alive aged 55. Recurrence
22	"	"	46	60	63	
23	"	"	46	63	73	
24	Miscellaneous	"	48	66	69	
25	Metropathia	Radium	50	51		Not followed up
26	Miscellaneous	Surgery	52	59	60	
27	Fibroids	"	55	64	67	
28	Prolapse	"	60	61	65	
29	Fibroids	"	63	64		Alive aged 85. No recurrence
30	Miscellaneous	"	67	85	87	
31	"	"	70	75	77	
32	Carcinoma of cervix	Radium	71	74	75	

2. *Age of Onset*.—The Table shows the age at castration and the age at onset of carcinoma, the limits of which are 35 to 85 years. There are seven cases between 50 and 55 years and nine between 60 and 65. These are the same as the highest figures for carcinoma of the breast in non-castrated subjects, but with a particular predilection for the 55 to 65 age group.

3. *Interval Between Castration and the Onset of Carcinoma*.—This ranged from two months to 24 years. In nine cases only was it less than five years, and it must be admitted that the cancer might have already been established at the time of castration. In 23 cases the interval was over five years.

4. *Means of Castration.*—These are shown in the Table. In seven cases castration was performed by irradiation (three by radium and four by x rays) and was followed by amenorrhoea when done before the menopause.

5. *Indications for Castration.*—In 19 cases castration was performed for fibroids or metropathia haemorrhagica. In 16 of these cases the procedure was carried out before the age of 48. There was one case of bilateral pyosalpinx (age 42), one case of prolapse (age 60—vaginal hysterectomy performed), two cases of carcinoma of the cervix, and one case of recurrent tumour of the ovary that was operated upon when the patient was aged 32 and 43. (This appeared as a solid tumour, the exact nature of which it was impossible to determine.) Eight cases were castrated for miscellaneous reasons.

6. *Influence of Age at Castration on the Interval before the Appearance of Carcinoma.*—It is impossible to correlate the age at castration with the interval before the onset of carcinoma. One can only observe that when castration is performed after the age of 50 the interval is often short (four cases out of eight). In 16 cases in which castration was performed during the menopause, between 40 and 50 years of age, the interval was usually long. In only two cases was it less than five years, and these two patients survived longer than five years.

7. *Types of Carcinoma.*—When first examined the patients presented carcinomas that could be classified as follows: grade 1, 9 cases; grade 2, 11 cases; grades 3 and 4, 9 cases; not precisely classified, 3 cases. Among the nine advanced types five had developed in less than six months. Only one had developed over a period of 10 years, after the age of 45; this patient had undergone castration by x rays at 38. No comment need be made concerning the morphological type or histological picture of these carcinomas. Only one was of the endocrine type.

8. *Mode of Development of Carcinomas.*—These carcinomas appeared to be particularly malignant. Of 32 patients one was not followed up, one survived for two years, two survived three years and now show evidence of recurrence, and four survived up to 10 years. Of the 24 patients who died of carcinoma, five survived five years after treatment. These were five women castrated at an early age (28 to 46). One (Case 1) had been operated upon two years after the appearance of the tumour. The condition recurred in the sixth to the ninth year after treatment, in the form of metastases in the lungs or widespread metastases in the vertebrae. On the other hand, seven patients out of 24 died in less than a year. Among these there were two with grade 1 carcinomas; both were castrated at the age of 32 and developed carcinoma at 35 and 53. The other five patients had grade 4 carcinoma which developed in less than six months and permitted only palliative treatment.

9. *Remarks on Case Histories.*—The effect of treatment must be taken into account in deciding the length of time during which the carcinomas developed. Apart from one case which was treated by a combination of surgery and irradiation, all the others (i.e., 23) that were suitable for radical treatment underwent Halsted's operation (with the exception of one patient with grade 1 carcinoma treated by local mastectomy). Four patients survived up to 10 years without recurrences among these 23 cases, giving one of the worst statistical results in surgery.

Some cases seem to merit special mention: (a) in two definite cases (carcinoma of the cervix) and in one probable case (recurrent tumour of the ovary) castration was indicated for malignant tumour of the genital tract; (b) in 19 cases out of 32 castration was performed for a fibroid

or for hyperplasia of the uterus; (c) nine post-menopausal cases were retained in the series because many pathologists consider that even in these circumstances castration still has a favourable action. No conclusion can be drawn from my own observations.

In some cases there are circumstances that I consider to be especially unfavourable: one case had previously undergone a biopsy and had been treated with small doses of testosterone; after castration two cases developed goitres, one of which was toxic (these were removed); and in one case the woman's mental condition (neurasthenia) might have been responsible for the rapid development of the growth.

Comment

The study of these 32 cases demonstrates the relative rarity of carcinoma of the breast in castrated women. The figure arrived at (1.6%) agrees with the figure of 1.5% that Herrell (1937) has established. He included benign growths in his series, and showed that in a significant number of patients dying of non-cancerous conditions the frequency of antecedent castration was 15.4%. However, although rare in castrated women, cancer does occur. Interpretation of a limited number of results is always hazardous, and these observations are mainly set down for the purpose of recording the facts. It is, however, obvious that in this series the age of onset of carcinoma is relatively late, and that the number of patients above the age of 60 is significantly high. It is particularly interesting to note that when castration was performed between the age of 40 and 50—at the age when the amount of circulating folliculin is considered significant—carcinoma of the breast appeared in general late (in one case the interval reached 23 years), and in all cases the development of the carcinoma was rather slow, even in cases of early onset.

The large number of cases of highly malignant carcinoma, in young as well as old women, is surprising. It is on this point possible to invoke not only the earlier experimental work of Cori and Murray, referred to by all surgeons and radiotherapists supporting the principle of castration, but also the more precise results obtained by other workers. The liberation of the growth hormone of the pituitary after castration has been demonstrated by Sauerbruch and Knake (1937). The favourable action of the gonadotrophic hormone on the growth of tumours of an ovary, the follicular secretion of which has been neutralized by splenic implantation, has been demonstrated by Penchar and Biskind (1947). One should perhaps attribute to an action of this sort the rapid growth and early onset of mammary tumours after castration and the unfavourable influence of treatment of a goitre in two cases.

At the same time it is well known that the menopause, natural or artificial, does not always suppress the appearance of folliculin in the circulating blood, and endocrinologists have occasionally been able to discover the presence of significant levels. The discovery of hyperplasia or adenomas of the suprarenal by Wooley and Little (1945) in mice after castration at birth, and by Gardner (1942) in older animals, shows that probably it is this gland that ensures the secretion of folliculin after the castration, and in the experience of these authors the frequency of spontaneous carcinoma of the breast is not altered.

The age at which castration is performed is certainly highly important, and the appearance of extragenital folliculin capable of producing carcinoma of the mammary gland is probably not so rapid in castrated women in the stage of hyperfolliculinaemia. I present this simple theory to explain the relative benignancy of carcinoma of the

breast occurring after castration at the menopause. This hypothesis stands to be confirmed or disproved by frequent estimations of the amount of folliculin circulating during the years following castration. Since comment on these anatomical and clinical findings can be made only with the help of experimental data, it is important to measure here the extent of our ignorance in this field. It must be admitted that three factors are undoubtedly present at the time of the appearance and development of mammary carcinoma—the milk factor (Bittner's mammary tumour inciter), the genetic factor, and the hormonal factor. Of these the clinician knows only one. Wooley and Little, for example, have convincingly demonstrated that only certain strains of mice develop suprarenal hyperplasia after castration, and van Gulik, Korteweg, and Muilbock, of Amsterdam, have shown, following the work of Lacassagne (1939), that sensitivity to oestrone varies according to the strain studied.

Conclusions

Until clinicians possess as many data concerning their patients as experimental workers have concerning their mice, castration by surgery or irradiation will never become a therapeutic procedure the efficacy of which can be guaranteed. On the contrary, there are perhaps cases where sterilization will have harmful effects. From the practical point of view these and other observations on castration performed for carcinoma of the breast, either already treated or first seen in an advanced stage, leads to the following conclusions.

(a) When carcinoma of the breast begins after castration, or even in spite of castration, the prognosis should be regarded as bad unless castration was performed near the time of the menopause. Castration has therefore, above all, a value in prognosis.

(b) Routine castration after treatment of the carcinoma is not a guarantee against later manifestations of the malignant condition. The problem is evidently not the same as in the cases discussed here, since the mammary tumour has been removed or irradiated. The point is to assure prophylaxis against local recurrence or metastases to bones or viscera. The sensitivity of these different sites to the action of hormones is very variable, and there is no proof that all of them are likely to be influenced. We know, for example, that a recent case of surgical castration, done shortly after combined surgical and x-ray treatment for carcinoma of the breast in a woman of 34, was followed after three months by the appearance of extensive mediastinal and pulmonary metastases. Recently Rudler reported similar cases at the Académie de Chirurgie. The fact that castration, advocated more than fifty years ago by Shinzinger and Beatson, has never been generally accepted as a favourable measure is proof of its relative ineffectiveness. At present the results reported by Horsley (1947) are often quoted; he combined surgical castration with treatment of the primary lesion and obtained excellent results over a period of five years. I think that the restricted number of these cases and the follow-up period of five years render these results open to criticism, and observation of our own cases castrated at the menopause shows that the value of this procedure can be judged only after an interval of at least ten years.

(c) Castration by surgery or irradiation in advanced carcinoma of the breast has given us two good temporary results (of 3 to 13 months) in ten cases in which the castration was performed surgically; of 28 cases in which castration was performed by irradiation 14.39% showed some degree of remission. Cases of highly malignant carcinoma appearing in recently castrated young women make us consider the possibility of failure of castration in similar circumstances.

However, the immediate favourable effects, even on the day of operation, on the pain of vertebral metastases or on the lymphatic infiltration in the mammary region, lead one to envisage a special neuro-hormonal or vasomotor effect of castration rather than a long-lasting endocrine effect.

Surgical castration has, especially for me, an academic interest, since on four occasions out of ten I have found metastases from the mammary tumour in the ovary. In these four instances manifestations of malignancy were severe, and it is possible that the occurrence of metastases in the ovary brought about an exacerbation of the condition. This is a valuable pathological argument in favour of systematic castration after treatment of carcinoma of the breast, but the endocrine problem will not be settled on this single fact. Thus, although there still exist some reasons for castration in carcinoma of the breast, the prognosis of this condition after castration should remain very guarded.

Summary

Thirty-two cases of carcinoma of the breast have been observed after castration by surgery or irradiation. They represent 1.6% of a series of 2,000 cases. Only four of these patients have survived for ten years without recurrence. Many tumours grew rapidly despite castration. The longest interval before the appearance of carcinoma was in women castrated between the ages of 40 and 50. Some comments are made and conclusions reached on the value of castration in cancer of the breast.

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CONGENITAL HEMIATROPHY ASSOCIATED WITH OTHER CONGENITAL DEFECTS

BY

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Minimal body asymmetry is very common in human development. Halperin (1931), in discussing normal asymmetry, states that the left side of the body is slightly larger than the right, particularly the cerebral hemisphere, skull, face, leg, and breast. When the inequality is such that it is noticed at or soon after birth it constitutes one of the rarest congenital abnormalities. The case reported here was associated with partial dental aplasia, cutaneous pigmentation, and talipes equinus.

Case Report

A girl aged 3 years 2 months was admitted to hospital in status epilepticus. Subsequent investigation showed that this was due to whooping-cough with bronchopneumonia. The status epilepticus was followed by a left-sided hemiplegia, which cleared up completely after five days. The cerebrospinal fluid was normal. The Wassermann reaction was negative in mother and child.

The patient was a full-term second baby, and pregnancy and labour had been normal. The birth weight was 8 lb. (3.6 kg.). The child was bottle-fed. The father developed shingles about one week after the estimated date of conception. Both parents are alive and well. There is no familial disease or abnormality. At birth the child exhibited a vesicular eruption on the left leg and on the dorsum of both hands. This condition lasted about four months and healed with scarring, particularly on the left leg. The aetiology of this eruption is uncertain and may have been a bullous impetigo. Brown pigmentation of the skin was also present at birth, and it has not altered in character or distribution.

When the child was 3 months old the mother noticed that the left leg was shorter than the right. At 1 year the child walked with a painless limp, and the left leg was considered to