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PHEOCHROMOCYTOMA: A FAMILIAL TUMOR

A STUDY OF ELEVEN FAMILIES

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At least twenty-one kindred representing fifty-nine histologically proven cases of pheochromocytoma have been reported in the literature (ref: 1 - 24). Eleven of these fifty-nine individuals had an associated carcinoma of the thyroid gland and a lesser number had parathyroid tumors. (See Table I)

Five percent of the reported pheochromocytomas have had a familial association.[1] Such estimations have been admittedly gross due to the fact that the familial nature of this tumor first came to light only twenty years ago. Judging from published data, numerous authors appear to lack cognizance of the familial concentration shown by this tumor.

The actual proportion of hereditary pheochromocytomas is unknown. Probably it is higher than published reports indicate since such factors as the time needed for a familial tumor to become manifest in successive generations, the generally poor knowledge most patients have of their family medical history and the difficulty — if not the impossibility — of ascertaining with certainty the cause of death of long-deceased individuals, militate against recognition of familial prevalence.

Twenty-nine cases of pheochromocytoma have been seen at the Henry Ford Hospital since 1951. This study consists of a retrospective survey of eleven families of these patients. The co-operating patients and their relatives sought out other relatives, family physicians, family bibles and other familial depositories of information in an attempt to determine the state of health of living relatives and the cause of death of deceased family members. Physical examinations were done on those relatives who had a suggestive medical history and who could or would come to the hospital for examination. Pharmacological screening tests (histamine, regitine

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Table I

case number	family	sex/age	relationship	site	reference
1.	A	f - 18	———	bilateral	(2) Fraenkel
2.	A	m - 50	nephew (case 1)	bilateral	(3) Lohmann
3.	A	f - 39	niece (case 1)	bilateral	(4) Volhard
4.	A	m - 44	nephew (case 1)	bilateral	(3) Lohmann
5.	B	f - 26	———	bilateral	(5) Calhins and Howard
6.	B	f - 17	niece (case 5)	bilateral	(6) Hyman and Mencher
7.	C	f - 18	———	bilateral*	(7) (8) Manning et al. Roth et al.
8.	C	f - 28	sister (case 7)	bilateral	(7) (8) Roth et al.
9.	C	m - 25	brother (case 7)	bilateral	(7) (8) Roth et al.
10.	D	m - 15	———	left	(9) Young and Murray
11.	D	f - 12	sister (case 10)	left	(9) Young and Murray
12.	E	f - 18	———	bilateral	(10) Kelsall and Ross
13.	E	f - 14	sister (case 12)	bilateral	(10) Kelsall and Ross
14.	F	m - 6	———	right	(11) Cone et al.
15.	F	f - 26	aunt (case 14)	———	(11) Cone et al.
16.	F	m - 16	son (case 15) cousin (case 14)	———	(11) Cone et al.
17.	G	f	———	bilateral	(11) Cone et al.
18.	G	f - 8	daughter (case 17)	bilateral intrathoracic	(11) Cone et al.
19.	G	f - 6	daughter (case 17)	right & bifurcation of aorta	(11) Cone et al.
20.	H	m - 26	———	left	(12) Greenberg and Gardner
21.	H	m - 3	son (case 20)	left	(12) Greenberg and Gardner
22.	I	m - 31	———	aortic bifurcation	(13) Cook et al.
23.	I	f - 42	sister (case 22)	aortic bifurcation	(13) Cook et al.
24.	J	m - 57	———	bilateral	(14) Carmen and Brashear
25.	J	m - 22	son (case 22)	right	(14) Carmen and Brashear
26.	J	f - 17	daughter (case 22)	left	(14) Carmen and Brashear
27.	K	f - 58	———	left	(15) Hradec
28.	K	m - 36	son (case 27)	left	(15) Hradec
29.	K	m - 32	son (case 27)	right	(15) Hradec

Table I (continued)

case number	family	sex/age	relationship	site	reference
30.	L	m - 62	———	bilateral*	(16) Smits and Huizenga
31.	L	m - 31	nephew (case 30)	bilateral	(16) Smits and Huizenga
32.	L	m - 30	nephew (case 30)	left	(16) Smits and Huizenga
33.	L	f - 15	niece (case 30)	right	(16) Smits and Huizenga
34.	M	m - 57	———	bilateral	(17) Hill and Smith
35.	M	f - 17	daughter (case 34)	left	(17) Hill and Smith
36.	M	m - 20	son (case 34)	right	(17) Hill and Smith
37.	N	f - 32	———	bilateral*	(18) Nourok
38.	N	f - 33	daughter (case 37)	bilateral*	(18) Nourok
39.	O	m	———	bilateral	(19) Finegold and Hadded
40.	O	m	son (case 39)	bilateral*	(19) Finegold and Hadded
41.	P	m - 55	———	right*	(20) Cushman
42.	P	m - 32	son (case 41)	left*	(20) Cushman
43.	Q	m - 34	———	left	(20) Cushman
44.	Q	m - 13	son (case 43)	right (2)	(20) Cushman
45.	Q	m - 17	son (case 43)	bilateral	(20) Cushman
46.	Q	m - 11	grandnephew (case 43)	bilateral	(20) Cushman
47.	R	m - 15	———	bilateral	(21) VonHagon and Barrows
48.	R	f - 13	sister (case 47)	right	(21) VonHagon and Barrows
49.	S	m - 21	———	right + extra a	(22) Tisherman
50.	S	m - 21	1st cousin (case 49)	right	(22) Tisherman
51.	S	f - 6	niece (case 50)	pre-aortic	(22) Tisherman
52.	S	m - 16	grandnephew (case 54) son (case 55)	left	(22) Tisherman
53.	S	m - 37	nephew (case 54)	left adrenal	(22) Tisherman
54.	S	m - 54	uncle (case 53) 2nd cousin (case 49, 50)	left adrenal	(22) Tisherman
55.	T	f - 27	———	bilateral*	(23) Schimke and Hartmann
56.	T	f - 18	niece (case 55)	bilateral*	(23) Schimke and Hartmann
57.	T	m - 39	cousin (case 55)	bilateral*	(23) Schimke and Hartmann
58.	U	f - 28	———	bilateral*	(23) Schimke and Hartmann
59.	U	m	brother (case 58)	———	Frunstein and Finkelstein

*also had cancer of the thyroid gland.

tests) and/or catecholamine analysis of urine specimens were done on those relatives in whom physical examination demonstrated signs of symptoms suspicious of pheochromocytoma. Using these methods, the health status of 253 relatives, living and dead, of pheochromocytoma patients was determined.

Findings:

Seven of twenty-two parents of pheochromocytoma patients had had hypertension, two had had diabetes. Of forty siblings surveyed, four were found to have hypertension and two to have diabetes. Nineteen children of pheochromocytoma patients were surveyed and two cases of hypertension were found. Altogether, thirteen instances of hypertension and four cases of diabetes mellitus were found in eighty-one close relatives of pheochromocytoma patients. No other significant pathology was discovered. Twenty-eight of these individuals were examined clinically by the authors.

Family studies: (See Diagram p. 471)

Family I:

A girl, eighteen years old, from whom a pheochromocytoma had been successfully removed, reported a brother aged 23 who had been diabetic since age 17. Examination of the brother and other family members failed to disclose evidence of pheochromocytoma.

Family II:

A middle aged woman who died of complications of pheochromocytoma had a father who had died at age 59 following a cholecystectomy, because of uncontrollable diabetes. The family physician, when interviewed, possessed no evidence suggestive of pheochromocytoma in his case record. Autopsy had not been performed. Her mother had been hypertensive and died accidentally at age seventy-five. Her paternal grandfather, diabetic, had died of "sun-stroke", age fifty. The patient's sister was examined and tested for pheochromocytoma with negative results, as was a niece.

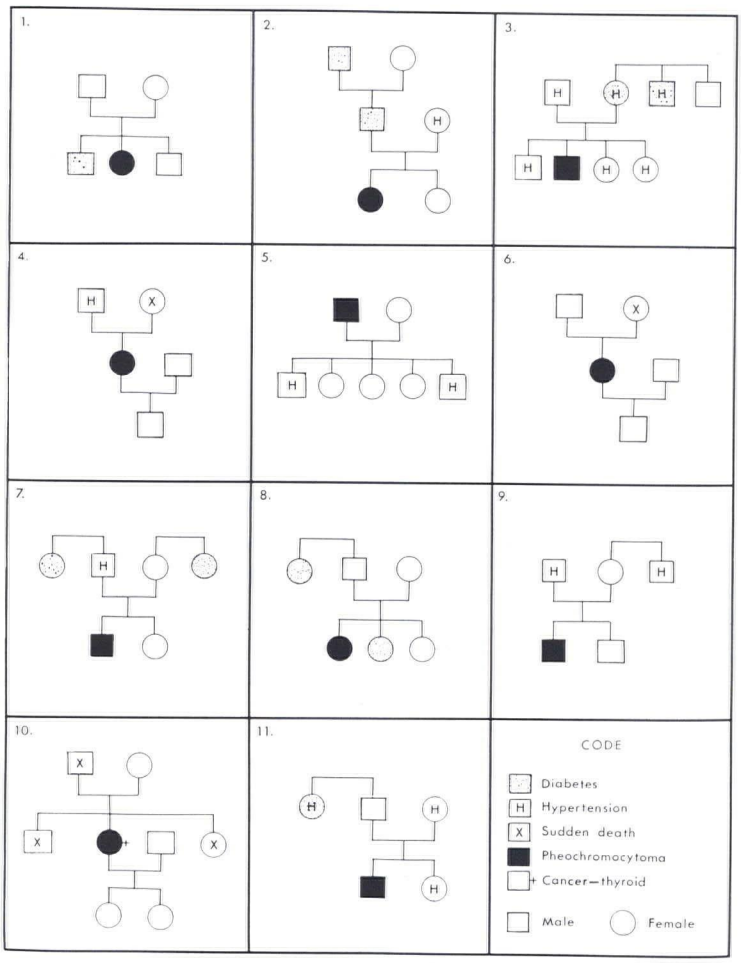
Family III:

A middle aged man died of complications of undiagnosed pheochromocytoma. Three siblings were reported to be hypertensive by his wife, one of whom was tested and found to be negative for evidence of pheochromocytoma. His father had died at age sixty-five of a cerebral hemorrhage and "blood pressure so high it couldn't be read" and his mother had died at fifty-two of uremia, cardiomegaly, diabetes and hypertension. A maternal uncle had died at age eighty of diabetes and hypertension. None of these suspect relatives had been autopsied.

Family IV:

This middle aged negro woman, despite the removal of a pheochromocytoma still displays mild hypertension (150/100), but has no evidence of recurrence of tumor. Her father is hypertensive. He declined examination. She reported that ten siblings and fifty-five nieces and nephews are living and well.

FINDINGS IN 11 PHEOCHROMOCYTOMA FAMILIES
(partial representation)



Family V:

This sixty-three year old man who died of complications of pheochromocytoma had four children. There was no history of suspicious illness in his parents. Three of his four children, including one hypertensive, were examined and tested. No evidence of pheochromocytoma was found. The possibility of this tumor has not been excluded in the remaining son, who is hypertensive.

Family VI:

This middle aged woman has mild (140/100) hypertension three years after removal of a pheochromocytoma without evidence of recurrence. She denied related illness in her parents or her child. Her mother had died, aged forty-eight, of peritonitis. No autopsy.

Family VII:

This middle aged man, childless, had had a pheochromocytoma removed four years previously and now has mild hypertension (150/95) with negative tests for recurrence. His father died of cerebral hemorrhage and hypertension at age sixty-nine and his paternal aunt died of diabetes at age sixty-five. Diabetes was also diagnosed in a maternal uncle who had died of cancer of the liver at age sixty-eight. None of these three relatives were autopsied.

Family VIII:

This forty-two year old woman is living and well two years following the removal of a pheochromocytoma. Her diabetic maternal aunt was not able to come for examination, but reportedly has no hypertension. A fifty year old diabetic sister was examined with negative tests for pheochromocytoma as also was her forty year old sister, a woman with emotional instability similar to that which the patient had exhibited prior to removal of her tumor.

Family IX:

This thirty-three year old man is well and normotensive nine years following removal of a pheochromocytoma. His father, a hypertensive, refused to come for examination. His paternal grandfather had died of a CVA at an elderly age. A maternal uncle is reportedly hypertensive but the patient's mother is living and well.

Family X:

This middle aged woman presented clinically with Cushing's syndrome but was found at post-mortem examination to have bilateral pheochromocytomata, multiple parathyroid adenomas and metastatic carcinoma of the thyroid gland (medullary type,

previously resected) to the liver and lungs. Her father had died at age thirty-three of "sun-stroke". A brother had died at thirty-one of a perforated ulcer and a sister had died at thirty-three following a gynecological operation. None had been autopsied. Both daughters of this patient were examined and found to be free of symptoms of either pheochromocytoma or thyroid malignancy.

Family XI:

This middle aged man had had bilateral pheochromocytomas removed. Presently, he has evidence of recurrent tumor. His hypertensive sister had negative pharmacological tests and catecholamine studies. The patient's mother had died at age fifty-eight of high blood pressure. She had suffered from severe headaches for approximately eight years prior to her death. Unfortunately, no autopsy had been performed.

Comment

Pheochromocytoma may be either familial or sporadic. Some of the sporadic cases may represent new mutations and eventually give rise to familial pheochromocytomata.

The object of the present study was to determine, in a small series, what percentage of pheochromocytoma cases might be of familial origin. While no definite pheochromocytomas were found among the more than two hundred relatives surveyed, the frequency of familial incidence remains in doubt. The possibility of pheochromocytoma cannot be excluded in sixteen relatives from nine families, who had had symptoms compatible with those produced by these neoplasms.

Family X, one member of which had developed neoplasms of the adrenal, thyroid and parathyroid glands is of particular interest. The sudden deaths of the patient's father and two siblings (ascribed to other causes) is suggestive of pheochromocytoma which is notorious in this respect. Two daughters of this patient, living and well, have been instructed concerning the need for periodic examinations.

Many of the problems inherent in determining the true familial incidence of any disease were encountered in this study.

1) Most patients had an appallingly poor knowledge of their family medical history. Such vague causes of death as "old age", sun-stroke, natural causes, childbirth and operations were frequent. Autopsy or medical records concerning such cases were non-existant or unavailable in most cases. Many ancestors and near relatives of our patients "died in the old country." Unfortunately, most of these old countries have since become new countries, discarding not only old ideals, traditions and socio-economic systems but medical records as well.

2) Familial diseases, excepting those which become apparent in early childhood, require many years for manifestation of their familial character. Lohmann,[3] in 1950,

investigating the occurrence of pheochromocytomata in three siblings, discovered that these patients were related to the original pheochromocytoma patient described by Fraenkel in 1886.[2] Similarly, twenty-two years elapsed between the detection of pheochromocytomata in a mother and her daughter reported by Nourok.[18] Clearly, the fact that the disease has not appeared in relatives of our probands to date does not mean that it may not do so in the future.

A factor which leads to overestimation of the familial incidence of this tumor is the tendency to accept suggestive clinical evidence without pathological confirmation as indicative of the disease in families of probands. In at least four instances, clinical evidence led us to a high degree of suspicion concerning the presence of a pheochromocytoma in a sibling of a patient. In all four cases, however, our suspicions were proven false by appropriate pharmacological and chemical tests.

Diabetes was present in six families and hypertension in seven. The significance of these findings is uncertain. However, these families do appear to have an abnormally high incidence of these two diseases.

Smits and Huizenga[16] studied a large family of over sixty members in which they found pheochromocytoma in four persons and probable pheochromocytomata in ten others. They concluded that the mode of inheritance of pheochromocytoma could be explained by the presence of one dominant gene as the etiological factor. How many of Smits and Huizenga's ten "probable" cases would have been found positive for the diagnosis on direct test is doubtful, in view of our experience with similar patients. Until it is possible to gather more direct evidence, it is best to reserve judgement regarding the specific mode of inheritance.

Tisherman et al[22] surveyed 199 members of a family and found seven proved and one probable pheochromocytomata in seven members, hypertension of unestablished origin in thirty others, cafe'-au-lait spots over 1.5 cm. in diameter (possible formes frustes of neurofibromatosis) in twenty-two, extensive hemangiomas in two and Hippel's disease in two. In addition, they suggested an association between pheochromocytoma and congenital cataract.

A recent review by Sapira et al[25] of pheochromocytoma occurring in association with thyroid carcinoma (Sipple's syndrome)[26] calls attention both to the high incidence of familial pheochromocytomata (six of eighteen patients had a family history of pheochromocytoma) and the high incidence of bilateral adrenal tumors (thirteen out of eighteen) in these cases.

More recently, Schimke and Hartmann[23] reported two additional cases of pheochromocytoma and thyroid carcinoma and provided further data on a case previously reported by Beer. In addition, they[23] discovered that previous familial case reported by Grunstein and Finkelstein,[24] originally thought to have bilateral pheochromocytomata metastatic to the thyroid, had, in fact, bilateral pheochromocytomata and a

typical amyloid producing medullary carcinoma of the thyroid. This uncommon type of thyroid carcinoma has been found in a clear majority of thyroid malignancies associated with pheochromocytoma.

An additional case of bilateral pheochromocytoma, medullary carcinoma of the thyroid and multiple parathyroid adenomata (see Family X) has been encountered in our experience and will be reported in detail elsewhere.[27]

Adding the above cases to previous experience, we find that eighteen of the twenty-two reported cases of pheochromocytoma associated with thyroid carcinoma were bilateral. It should be noted that two of the four patients with unilateral tumors were alive at the time of publication and could conceivably develop contralateral adrenal tumors in the future. Sixteen of the twenty-three reported cases of Sipple's syndrome were females but further reports are needed before the significance of this sex distribution can be evaluated.

Schimke and Hartmann[23] maintain that the thyroid carcinoma occurring with familial pheochromocytoma is invariably of the medullary type and that there is strong evidence supporting the contention that these two tumors are products of the same genetic defect.

Some authors[18,28] have suggested that the association of pheochromocytoma with thyroid carcinoma and, less often, with parathyroid adenoma might represent a variant of the multiple endocrine adenomatosis (MEA) syndrome. Schimke and Hartman point out that the absence of involvement of other endocrine organs (pancreas etc.) in the thyroid malignancy- pheochromocytoma syndrome, the low incidence of thyroid malignancy in the MEA syndrome, and the lack of increased peptic ulcer incidence in association with pheochromocytoma, suggests that the pheochromocytoma- medullary thyroid carcinoma syndrome is a genetically distinct entity.[23]

The slight male preponderance (34 to 25) in familial pheochromocytoma is probably of little significance. The high incidence of bilateral tumors (23 out of 59) is consistant with the observation that inherited tumors tend to multiplicity. It is noteworthy that familial pheochromocytomata seem to occur at an earlier age than the sporadic form, only 9 of 59 familial cases being past the age of forty.

More important, perhaps, is the tendency for familial pheochromocytomata to appear at an earlier age in each succeeding generation, (see Table II). This tendency to an earlier phenotypic manifestation of genotypic status has been noted in other familial malignant tumors, such as carcinoma of the breast. The factors underlying this phenomenon, when understood, will undoubtedly contribute greatly to the knowledge and understanding of individual resistance to neoplastic disease and the nature of the neoplastic process.

It is clear that in some families, pheochromocytoma is highly concentrated and follows a pattern of incidence consistant with dominant gene inheritance.[16]

However, in some families, parents of uniformly affected siblings have not manifested the disease.

If all cases of pheochromocytoma were inherited on a dominant non-sex linked basis, our direct examination of twenty-five siblings of probands in the tumor age group should certainly have revealed some additional cases. The fact that none of our probands have demonstrably diseased siblings indicates that, while familial determination may underlie some cases, it certainly is not responsible for all.

Our experience favors the hypothesis that sporadic cases are more frequent than familial cases or else that, if the disease has a genetic etiology, the penetrance of the gene and its phenotypic expression are subject to suppression by other biological factors. In this connection it can be noted that only four neoplasms of man are known to be inherited as dominant conditions and all of these manifest themselves in early childhood or adolescence. Pheochromocytoma occurrs in childhood in only ten percent of cases.

The occasional appearance of pheochromocytoma in association with familial neurofibromatosis, von-Hippel-lindaus' disease and familial medullary carcinoma of the thyroid,[1,25,29] also casts doubt on the hypothesis that the inheritance is of the simple dominant pattern.

Genetically linked neoplasias in general have been found to be the result of multiple etiologic determinants, and the common variety of pheochromocytoma would appear to be no exception to this rule.

Based upon the knowledge obtained in these studies, the following conclusions may be drawn:

1) Familial pheochromocytoma is a condition of high penetrance but many cases appear to be sporadic or non-familial in character.

2) Nevertheless, all pheochromocytoma patients (particularly those with bilateral tumors) and their families should have careful periodic examinations with special attention to the adrenal, thyroid and parathyroid glands because of the demonstrated familial concentration of the disease in some families. The possible concurrence of neuroectodermal disorders including neurofibromatosis, von Hippel-Landau's disease and congenital cataracts should be kept in mind.

3) A thorough search for pheochromocytoma should be made in all patients and families in whom the diagnosis of neurofibromatosis or medullary carcinoma of the thyroid gland has been detected.

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Table II

AGE AT DISCOVERY OF FAMILIAL PHEOCHROMOCYTOMA RELATED TO FAMILY GENERATION

	GENERATION		
*FAMILY	I	II	III
A	18	39-44-50	
B	26	17	
F	26	16-6	
G	25 +	8-6	
H	26	3	
J	27	22-17	
K	58	36-32	
L	62	31-30-15	
M	57	20-17	
N	32	33	
P	55	32	
Q	34	17-13	11
S	54	37-21-21	6-11
T	39-27	18	

* see Table I.

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