Ganglioneuroblastoma was diagnosed in 5 patients with regional disease. Three received radiotherapy after partial excision in 2 and total excision in 1; no radiotherapy was given to 2 patients with excision of all visible tumor. These small numbers do not permit an accurate assessment of the value of radiotherapy for ganglioneuroblastoma.

Present chemotherapeutic regimens utilized for neuroblastoma have not been notably successful. None of the drugs presently available seem indicated in patients with regional disease; none of the survivors in this group received chemotherapy. Such agents should be employed in the patients with disseminated disease in view of our salvage of 4 of 31 patients with distant metastases. Future improvement in treatment results will require either earlier diagnosis or the development of more effective chemotherapeutic agents.

SUMMARY AND CONCLUSIONS

The experience with neuroblastoma and ganglioneuroblastoma from 1952 through 1965 is reviewed. Factors associated with an improved prognosis include diagnosis before one year of age, mediastinal location, tumor maturation and lack of dissemination.

Radiation therapy appears to be the most important form of therapy in the patients with regionally contained neuroblastoma. Total tumor removal followed by radiotherapy is associated with an excellent prognosis, but total removal should not be attempted if the risks of the extended surgical procedure are increased.

Improvement in the survival rate awaits ... allowing earlier diagnosis and a more ... method of treating widely disseminated di...

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FAMILIAL NEUROBLASTOMA*

Report of a Kindred with *Multiple Disorders, Including Neuroblastomas in Four Sibli...

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ALTHOUGH neuroblastoma is a common tumor of childhood, it has rarely been reported to affect more than 1 member of a family. The present study was undertaken when we observed neuroblastomas in 3 of 4 siblings. We found that the mother was in her sixth month of pregnancy and was excreting abnormal amounts of urinary catecholamines. The infant born of this pregnancy was followed prospectively, and became the fourth affected sibling when she was discovered to have a mediastinal neuroblastoma at five months of age. The purpose of this report is to describe the findings in the family, to review previously reported kindreds and to discuss the implications of familial neuroblastoma.

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CASE REPORTS

CASE 1. Carol E., the mother, is a healthy, asymptomatic 30-year-old housewife of German ancestry. Her relatives (parents, 2 brothers, and 4 nephews and nieces) are healthy. A 5th nephew died of congenital heart disease associated with maternal rubella.

Physical examinations since April, 1963, when she was in

month of her 5th uneventful pregnancy, hac e re- normotensive, fair woman of average height and with no evidence of tumor or neurocutaneous dis- ally or radiologically.

James J. E., the father, a healthy 38-year-old man descent, has 3 large café-au-lait spots and mild excavatum. His report that these findings were com- his family led us to examine his 5 siblings and par- the positive findings that 3 of the father's siblings pectus excavatum, and all have cafe-au-lait spots (1 to 3 each over 1.5 cm in least didmeter), but none have tumors or hypertension. 1 brother has a cardiac without disability, and 1 sister has had 6 sponta- rtions. Among 19 live-born paternal nieces and nephews, 2 died of "prematurity"; 2 have had solitary skin lesions treated with dry ice. and I has pectus excavatum.

The children born to Carol and James E. are described below in order of birth, and the findings in affected siblings are summarized in Table 1.

CASE 3. James E. (C.H.O.P. 582141) was born on April 4, 1958. Laparotomies on April 7 and 13 for intestinal obstruction revealed aganglionosis of the ileum and colon. Despite ileosigmoidostomy and distal cutaneous ileostomy, obstruction persisted, and he died at the age of 26 days.

Post-mortem examination revealed a 3400-gm male infant without gross anomalies. There was a microscopic neuroblastoma in the medulla of one of the grossly normal adrenal glands.

TABLE 1. *Reported* Cases *of Familial Neuroblastoma.*

DATA	FAMILY HISTORY	BIRTH ORDER	SEX	AGE AT DEATH	LOCATION OF TUMOR		COMMENT
					SYMPATHETIC NERVOUS SYSTEM	OTHER SITES	
				yr			
nner[1]	.Negative	I	M	7/12	Rt. adrenal gland	Liver	
		2	F	4	Rt. adrenal gland	None	"Failure to thrive" for 2 yr; "diverticulum" of colon at autopsy.
	?	?	M	13	Lt. adrenal gland	Lymph nodes; bone.	"1 other child in family had multiple necroses of skull"
	?	I	F	?	?	?	"Died of disease that ran apparently same clinical course"
		2	F	2-1/2	Lt. adrenal gland	Liver; lymph nodes; kidneys.	
	Father: Mediastinal ganglioneuroma (?); 3 of 5 sibs died in childhood.	AI	M	2-8/12	Rt. & Lt. adrenal gland	Liver; lymph nodes; bone.	Only child of this marriage
	Mother: Histories unknown	B2	F	1-3/12	Rt. & Lt. adrenal gland	Liver; bone; pancreas.	Diffuse involvement of sympathetic ganglions; full sib B1 died at 3 mo of "malnutrition."
	Mother: Normal urinary catecholamines	1	F	1-3/12	Rt. adrenal gland	Liver; skin.	Many ganglion cells in tumor at autopsy
		5	F	12 (living)	? Lt. adrenal gland	Liver; lymph nodes; skin (40 nodules palpable at age of 2 days).	1 residual subcutaneous lesion present
l report:	Mother: Abnormal urinary catecholamines Paternal family: Has café-au-lait spots	I	M	1/12	1 adrenal gland *(in situ)*	None	Long-segment aganglionosis; patent ductus.
		3	F	2-4/12	Lt. & Rt. adrenal glands & thorax	? Lymph nodes; bone.	No autopsy
		4	F	1-1/12	Rt. & Lt. adrenal glands	None	Patent ductus; pulmonary hypertension; pyloric stenosis (?); atonic diplegia with gliosis.
		5	F	2 (living)	Rt. hemithorax	Bone marrow	Patient receiving chemotherapy & well

The small intestine was dilated up to the anastomosis, 120 cm beyond the ligament of Treitz. The distal ileum was 67 cm long and was collapsed. as was the colon. Aganglionosis of myenteric and submucous plexuses began 75 cm below the duodenojejunal junction, and extended to the anus. The ileum was devoid of nerve fibers. but the colonic plexus had a normal complement of fibers. The ductus arteriosus had an internal diameter of 0.2 cm (patency of possible significance in view of the presence of medial hypertrophy of the small pulmonary arteries).

CASE 4. James A. E., born in 1959, has had no serious illnesses. There is no evidence of tumor or anomaly on physical examination or on radiographs of the chest and abdomen.

CASE 5. Audrey E. (C.H.O.P. 628739) was born on November 26. 1960. A mass was palpated in the left side of the abdomen at 15 months of age, and resection of the left adrenal gland and biopsy of regional lymph nodes revealed neuroblastoma. Radiotherapy was administered, but 10 months later. the patient was referred to Children's Hospital of Philadelphia because of swelling below the right orbit.

On physical examination, in addition to a palpable lesion in the right zygoma, there was right inguinal adenopathy, and a bone-marrow aspirate contained a few tumor cells. Radiographs revealed a paravertebral mass extending from the right 6th to the 11th thoracic vertebra and a small area of calcific density in the right suprarenal area.

Despite treatment with mitomycin C, 5-fluorouracil and radiotherapy, lymphadenopathy increased. The patient died suddenly at home on March 11, 1963. No autopsy was performed.

CASE 6. Amy E. (C.H.O.P. 644678) was born on January 5, 1964, and treated for pneumonia and pyloric stenosis at 2 weeks of age. At 4 months of age, she was readmitted to the hospital with evidence of pneumonitis and pulmonary hypertension. for which she was referred to Children's Hospital of Philadelphia.

Physical examination revealed a listless. slightly cyanotic baby with scattered pulmonary rales and a transient systolic murmur. There was generalized hypotonia, with absence of corneal and deep tendon reflexes. The course was complicated by an apneic episode and generalized seizures on the 5th hospital day (requiring prolonged respirator therapy) and 2 episodes of diarrhea with hypernatremic dehydration. A retrocardiac radiodensity became apparent as pulmonary infiltrates cleared. Discharge diagnoses on July 10, 1964, were pneumonitis, possible congenital heart disease .and atonic diplegia due to anoxia or cerebritis or both.

On August 10 and November 19 and 28, 1964, and January 12, 1969, the patient was readmitted to the hospital. Respiratory distress, cyanosis and feeding difficulties recurred and progressed despite the use of digoxin, corticosteroids and postural drainage. Signs of pulmonary hypertension without murmur or decompensation, and of atonic diplegia. were present throughout the course. There was radiographic evidence of pulmonary congestion or infiltration, or both. on several occasions. Cardiac catheterization revealed no intracardiac shunt, but right ventricular hypertension and left atrial unsaturation were present. A later study outlined the ductus arteriosus, but the shunt at this level was insignificant. There was a gradual increase in the size of the retrocardiac mass, and a diagnosis of neuroblastoma was made. Gavage feeding and increasing oxygen administration were required until death on February 5, 1965.

Post-mortem examination revealed a thin girl 77 cm long and weighing 7800 gm, without external abnormalities. The lung contained no evidence of recent or old inflammation or vascular lesions. The ductus arteriosus was 0.4 cm in internal diameter, and there were no cardiac anomalies. Biventricular hypertrophy, more marked on the right, and generalized visceral congestion supported the clinical diagnosis of primary pulmonary hypertension with [illegible] monale

The retrocardiac mass was 3.0 cm in diameter, and had ruptured the sympathetic chain at the level of the 8th thoracic vertebra There was a similar mars 2.0 cm in diameter at the level of the 2d thoracic vertebra. In addition, there was a 22-gm mass, 4.5 by 3 by 3 cm. in the left and a [illegible] mass, 3 by 2 by 2 cm, in the right adrenal gland. Each of these was a neuroblastoma. Their locations suggested that each was a primary lesion

The gastrointestinal tract was grossly and histologically normal. Terminal necrosis and hemorrhage in the pancreas may have been related to steroid therapy or undetected invasion of the pancreas by the adrenal tumors.

The brain was atrophic (weighing 752 gm), and there was diffuse neuronal destruction and gliosis consistent with remote anoxic injury. The thoracic spine and spinal cord were grossly intact, and skeletal muscle was histologically normal. It appears, therefore, that hypotonia and areflexia were not the result of spinal-cord compression or myopathy but had a central basis, which may have antedated the 1st admission.

CASE 7. Laurie E. (C.H.O.P. 654664), born on [illegible] 1965, was admitted to the Clinical Research Center of Children's Hospital of Philadelphia 16 days later because of [illegible] family history. There were no positive physical findings. Radiographs of the chest and abdomen gave no evidence of tumor.

At 5 months of age she was readmitted to the hospital for study. The only complaint was anisocoria, present for several months. Physical examination revealed slight constriction of the right pupil without other signs of Horner's syndrome. Radiographs demonstrated a mass at the level of the 7th or 8th thoracic vertebra, with no evidence of intra-abdominal or skeletal lesions. A bone-marrow aspirate contained tumor cells suggestive of tumor. On January 19 the 2.2-cm thoracic mass was resected, and vincristine was given. Histologic examination confirmed that the tumor was a neuroblastoma and that there was no invasion of adjacent nerves, ganglions or lymph nodes.

The patient has been readmitted for study at intervals of 1 to 3 months. Anisocoria has subsided. Tumor cells have become less frequent but are still present in bone marrow aspirates. These cells and a transient rise in urinary catecholamine excretion (as discussed below), prompted the institution of treatment with vincristine and cyclophosphamide 6 months after operation. On the last admission (August 28, 1967) 1 year after institution of chemotherapy, the patient remained free of clinical or radiologic evidence of primary or metastatic tumor.

SPECIAL STUDIES

Urinary dopamine, norepinephrine, epinephrine, and 3-methoxy-4-hydroxymandelic acid (VMA) were determined by previously described methods,[6] and the results are shown in Table 2. The mother had abnormally high output of dopamine, norepinephrine and VMA during pregnancy, and these findings have persisted on 5 post-partum studies over a period of twenty-three months. Her parents and brother have normal catecholamine output, as do the father (James J.) and the healthy sibling (James A. E.), now eight years old. The VMA values in Audrey and Amy E. were obtained terminally, and showed significant elevations.[7] No abnormality of catecholamine metabolism was detected in urine of Laurie E. at birth, but output of dopamine, norepinephrine and VMA was modestly high when the neuroblastoma was discovered. After removal of the

TABLE 2. *Urinary Catecholamine Excretion in Family E.*

	AGE	STATUS	DATE	URINE VOLUME	DOPAMINE	NOREPINEPHRINE	EPINEPHRINE	VMA
	yr			*ml*	*μg/24 hr*	*μg/24 hr*	*μg/24 hr*	*μg/24 hr*
Normal	*Adult*	Healthy			249.1 ± 74.9	50.7 ± 15.7	7.1 ± 3.3	3192 ± 699
Maternal grandfather	66	Healthy	6/66	1440	244.7	82.94	7.49	1728
Maternal grandmother	55	Healthy	6166	595	96.8	46.89	2.62	1904
Maternal	33	Healthy	8/66	1170	170.8	51.48	6.08	1872
Child (father)	38	Healthy	4165	1060	153.1	40.3	3.4	1950
Child (father)	28	Pregnant	4/65	2390	1539.0	253.3	5.7	7170
		Postpartum	8165	1850	2679.0	370.0	–	9250
		Healthy	12/65	1380	2726.9	435.0	–*	13800
		Healthy	1/66	1160	1930.2	339.2	–*	8700
		Healthy	6/66	1280	1812.5	331.26	1.02	7680
	30	Healthy	3/67	3050		395.3	61	5185
	6-15	Healthy			169.3 ± 72.6	37.4 ± 16.6	4.8 ± 2.4	2373 ± 698
Child	6	Healthy	4/65	650	99.8	20.8	2.1	2544
	7	Healthy	6/66	440	126.1	38.90	4.05	800
	8	Healthy	8/67	790	151.7	20.86	9.79	
	2-3/12	Terminal neuroblastoma	2/63	?				6600†
	10/12	Mediastinal mass known	11/64	400				4400†
	<1	Healthy			60.9 ± 24.3	10.6 ± 3.4	1.3 ± 1.2	569 ± 309
	Newborn	Healthy	8/65	420	36.6	10.0	0.79	420
	5/12	Before operation	1/66	350	70.1	18.48	1.26	1400
		After operation	1/66	160	56.7	14.48	1.69	1280
	6/12	After operation	2/66	385	93.3	16.47	0.61	1155
	7/12	After operation	3/66	150	29.03	6.78	0.78	480
	10/12	After operation	6166	360	68.3	20.74	2.74	432
	11/12	After operation	7/66	160	49.9	18.37	0.58	1088
	1	On chemotherapy	8/66	110	22.5	8.10	0.48	308
	1-3/12	On chemotherapy	11/66	230	39.6	14.54	0.92	644
	1-7/12	On chemotherapy	3/67	575	111.8	20.24	2.99	1150
		On chemotherapy	6/67	370	96.0	8.29	2.52	752
		On chemotherapy	8/67	475	71.6	18.81	2.28	950

detected.
<1000 μg/24 hr <1 yr of age; <6000 μg/24 hr in all children.[7]

the values returned to normal levels. Five later they increased again, and fell upon tion of chemotherapy.

or tissue from Laurie E. was homogenized deproteinized in 10 per cent trichloroacetic The resulting extract was washed with anhyether, adsorbed on an alumina column, eluted 0.5 N acetic acid and then analyzed for norphrine and epinephrine, ferricyanide being used oxidant. The tumor sample weighed 0.8 gm contained 0.065 μg of norepinephrine. The pinephrine content in neuroblastoma varies from an 1.0 to 75 μg per gram of tissue, and cannot related with urinary catecholamine excretion sponse to therapy.

types of the parents and of Laurie E. are in both peripheral leukocytes and bone

m specimens obtained from the mother. and aurie E. two months after operation, were for nerve-growth-stimulating factor by Dr. Milton Goldstein.[8] No growth stimulation was demonstrated in the mother's serum, suggesting that her abnormal catecholamine excretion is not related to production of nerve-growth factor. Laurie E.'s serum exhibited + to ++ stimulation. This low titer probably reflected residual tumor, in view of the bone-marrow findings and subsequent rise in catecholamines.

DISCUSSION

Familial Neuroblastoma

To our knowledge, the kindred reported here is the first in which 4 siblings have had neuroblastoma, and the first in which a parent has been found to have abnormally high urinary catecholamine excretion. There are 4 reports in the older literature in which a second sibling was suspected[2,3] or proved[1,4] to have neuroblastoma. One of us (M.L.V.) has collaborated in the study of another family,[5] which included 2 affected children whose mother

has normal urinary catecholamine excretion. The only evidence of parental involvement in the older reports is Zimmermann's[4] case, in which the common father of affected half-siblings had an apparently benign mass in the posterior mediastinum. These 6 kindreds, summarized in Table 1, are the only ones we are aware of in the voluminous literature on neuroblastoma, but they are adequate to suggest that some neuroblastomas may be inherited.

Several genetic mechanisms might explain the distribution of affected members in these families. Autosomal dominant inheritance was suggested by Zimmermann: and this mechanism is believed to be the cause of most familial tumors. To explain the relatively large number of nonfamilial cases of neuroblastoma, including 3 examples of discordant twin pairs,[9] it must be assumed that many sporadic cases arise by mutation and represent lethal genes, or that the dominant gene has variable penetrance or expression. Thus, some families with more than 1 affected member may not be identified because the tumor is present as an *in situ* lesion, spontaneously regresses or matures into a benign tumor.[4,10] It is also possible that neuroblastoma represents a combination of genes controlling neural-crest development. The café-au-lait spots in the paternal members of the family reported here may represent a second genetic factor contributing to the incidence of tumor in the offspring.

It is of interest to compare neuroblastoma to pheochromocytoma, a more differentiated tumor having similar histogenesis and metabolic properties. Pheochromocytoma has been described in many kindreds, and is believed to have a dominant mode of inheritance, often in association with hereditary neurocutaneous or endocrine disturbances.[11-13] Neuroblastoma has been observed in patients with neurofibromas,[14,15] and tumors containing both neuroblastic and chromaffin elements have been described.[16] Such examples of the participation of neuroblasts in sporadic cases of neural-crest disease led Knudson and Amromin[15] to conclude that neuroblastoma might represent a dominant mutation. These authors predicted that spontaneously arrested cases of neuroblastoma (or related lesions) might be found among the relatives of patients with the disease. The data presented here fulfill this prediction, in that the father in Zimmermann's[4] report had a probable ganglioneuroma and Carol E. has abnormal catecholamine excretion. The corollary prediction, that survivors of neuroblastoma might have affected offspring, requires investigation. As neuroblastoma becomes less lethal with therapy, it should be possible to collect such data.

Neuroblastomain Situ

Beckwith and Perrin[17] defined neuroblastoma *in situ* as a discrete nodule of cytologically typical neuroblastoma, encountered only upon microscopical examination of adrenal glands from patients dead of other diseases. They estimated its frequency at about 1:200 autopsies of infants. Since overt neuroblastoma in the pediatric population was taken to occur in approximately 1:10,000 live-born children, and since in *situ* lesions were not encountered over the age of three months, it was evident that not all in situ lesions become overt neuroblastomas. One or all of the following explanations were suggested: the *in situ* lesion is not a neoplasm, but a transient fetal cell rest, despite its resemblance to neuroblastoma; the lesion is selectively distributed in the portion of the pediatric population dying in infancy; or it is a true neoplasm, which in most instances progresses (or matures into a benign lesion). The presence of a neuroblastoma in situ in James E., who had a lethal anomaly, and who had 3 siblings with overt neuroblastoma, favors the second and third hypotheses.

Relation of Neuroblastoma to Congenital Anomalies

Miller[18] was unable to demonstrate an unusual incidence of congenital anomalies in patients with overt neuroblastoma, although he recognized the theoretical likelihood of such a correlation. The presence of aganglionosis and patent ductus arteriosus, and perhaps some of the other lesions in the affected siblings described above suggests a developmental association between the anomalies and the neuroblastomas.

The relation of neuroblastoma to aganglionosis (an absence or failure of migration of parasympathetic neurons) is of particular interest, since the 2 lesions appear to be such dissimilar reactions of neural-crest cells. Passarge[19] has summarized the genetics of Hirschsprung's disease, noting its familial distribution expecially in long-segment disease, and its association with Down's and Turner's syndromes. Aganglionosis has been reported in an eighteen-year-old patient with pheochromocytoma and neurofibroma," and the embryologic relations between aganglionosis, pheochromocytoma and familial dysautonomia have been discussed by Boggs and Kidd.[21] James E. is the only patient we are aware of with aganglionosis (long segment) and neuroblastoma in situ. A patient with the classic form of Hirschsprung's disease and overt neuroblastoma has previously been reported from the Children's Hospital of Philadelphia.[22] The combination of aganglionosis with tumors of the sympathetic nervous system suggests a common cause acting through qualitative or temporal differences in the fetal parasympathetic (craniosacral) and sympathetic (thoracolumbar), neural-crest derivatives.

The relation between the neuroblastomas and the cardiovascular lesions in the siblings is unknown. It seems unlikely that tumor metabolites would cause persistence of the ductus arteriosus or pulmonary hypertension. Conversely, perhaps the cardiovascular lesions provide an anoxic stimulus to the sympathetic system, producing tumors in this family.

Folger et al.[23] have suggested that such a mechanism may explain the occurrence of pheochromocytoma in older persons with cyanotic congenital heart disease.

It has been proposed[24] that congenital heart disease is unusually frequent in patients with neuroblastoma *in situ*. Beckwith and Perrin[17] pointed out that the proportion of anomalies was only slightly higher in their 13 infants with neuroblastoma in *situ* than in controls, that the anomalies had no consistent pattern and that a large series of cases would be necessary for valid conclusions. Meanwhile, since patients with *in situ* lesions have, by definition, died of other diseases and since congenital anomalies (especially cardiac) account for most deaths in pediatric hospital autopsy populations of this age, the occurrence of neuroblastoma **in situ** in infants with anomalies must be interpreted with caution.

Significance of Abnormal Catecholamine Excretion

The mother of this family is unique in having persistently abnormal elevation of urinary dopamine, norepinephrine and VMA, and **4** children with neuroblastoma. She is also of great interest because of the lack of signs or symptoms of excessive pressor amine secretion, even in association with pregnancy. We have seen many normotensive children with similar excretion patterns in association with neuroblastoma. It is postulated that the absence of pressor effect is related to rate of turnover of catecholamine, abnormal storage in granules and degradation of pressor amines to inactive metabolites in the tumor cells.[26] "Silent" pheochromocytomas have been found at autopsy of normotensive patients, and it is not known if abnormal urinary catecholamine excretion is present in such cases. Usually, pheochromocytomas are not associated with high dopamine excretion unless they are malignant.[27]

It is possible that this mother has a small functioning tumor of neural-crest origin that has escaped detection to date. It is also possible that she has defective storage of catecholamines in the sympathetic nervous system, with resultant rapid turnover and increased urinary excretion of these compounds. It seems likely that a familial disorder of nervous tissue may be associated with abnormal catecholamine metabolism, for Smith and his coworkers[28] found an abnormal ratio of homovanillic acid to VMA in familial dysautonomia. Clinical similarities between dysautonomia and pheochromocytoma have also been described.[29] Although the histologic changes in the sympathetic and myenteric ganglions that have been reported in dysautonomia[30] were not observed in this family, Amy E.'s episodic and unexplained symptoms suggest autonomic imbalance akin to that disease.[31,32]

Whether the mother's abnormal catecholamine excretion is due to tumor or to a disorder of catecholamine metabolism, its relation to the tumors in her offspring does not appear to be humoral.[25] There is a report[33] of bilateral adrenal pheochromocytomas in an infant whose mother took a monoamine oxidase inhibitor and a sympathomimetic drug during her first trimester of pregnancy, but we know of no reports of the lesions described in family E. occurring in the offspring of mothers with known sympathetic tumors.

Many investigators have shown that abnormal catecholamine metabolism is present in association with neuroblastomas. However, Laurie E. is the first patient described with neuroblastoma whose urinary catecholamine excretion has been followed prospectively. No abnormality was detected in the neonatal period. Slightly high dopamine, norepinephrine and VMA excretions were observed just before excision of a small mediastinal neuroblastoma at five months of age. These values fell to normal after operation, and a second elevation five months later was considered an indication for chemotherapy. The lack of measurable catecholamine in the resected tumor is not unexpected. There is often little or no catecholamine in this undifferentiated tissue, probably for the same reasons there is little pressor activity."

SUMMARY

A family is reported in which the asymptomatic mother has abnormally high urinary excretion of dopamine, norepinephrine, and VMA, **4** of her **5** offspring had neuroblastomas and **2** of the affected siblings had other major diseases. These findings, together with other reports of familial neuroblastoma, are considered to suggest that this tumor may be inherited. It is proposed that the basic defect may be disturbed differentiation of the autonomic nervous system, including an abnormality **in** catecholamine synthesis or storage in the sympathetic nervous system.

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SPECIAL ARTICLE

NURSE CLINICS AND PROGRESSIVE AMBULATORY PATIENT CARE*

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THE increasing demand for health-care services in the United States has been documented in several studies. The obvious solution, more manpower in all disciplines, is somewhat unrealistic. In all probability, the demand for health services, as presently organized, cannot be met at the rate that current education programs in the health professions *can* be expanded or replicated.' There is considerable discussion regarding the delegation of certain aspects of medical care to new types of health professionals as a means of increasing the quantity of services available. Another possibility is to define more adequately the roles of existing disciplines, on the assumption that they might work together more efficiently in providing interprofessional care for a larger number of patients.

Although the hospital is the focus of medical care, the greatest demands for health services are made by vertical, rather than horizontal, patients. Inordinately large demands for ambulatory patient care are created by two groups of consumers. During the first few years of life, children must be seen frequently to provide optimal preventive care. At the other end of the life cycle of man, aging patients with chronic diseases accumulate. They too require frequent medical attention. Considering the "excessive" niedical care needs of these two segments of the population, it is not surprising that they have been the subjects of experimentation in the deliver! of services.

Projects have been described in which nurses have assumed some of the functions of physicians engaged in the practice of obstetrics and pediatrics.[2-4] With few exceptions, these programs have dealt with relatively normal infants and mothers. In addition, clinic-based projects using nurses for am-

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