DIAGNOSTIC AND PROGNOSTIC VALUE OF THE DETERMINATION OF URINARY OUTPUT OF VANILLYL-MANDELIC ACID IN TUMOURS OF SYMPATHETIC NERVOUS SYSTEM*

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The clinical differential diagnosis between benign and malignant tumours of the sympathetic system, and between tumours of the sympathetic system and other tumours in children often presents a definite difficulty. In the case of a posterior mediastinal tumour, it is almost impossible to recognize from clinical and radiological data alone a malignant neuroblastoma sympatheticum from a benign ganglioneuroma. The exact diagnosis between retroperitoneal neuroblastoma and Wilms' tumour often remains unsettled until surgical intervention. Therefore, we were in search of a laboratory test able to give us further information: the determination of the urinary output of 3-methoxy-4-hydroxy-mandelic acid, also named vanillyl-mandelic acid proved reliable.

This substance is a break-down product both of

adrenaline and noradrenaline (Fig. 1) and it is normally excreted in the urine at a steady rate (von Studnitz, 1960). The product is stable and its determination is relatively easy, which is not so for the determination of adrenaline and noradrenaline. Our work was based on the studies of von Studnitz and Hanson (1959a and b) and von Studnitz (1960). We undertook the determination of vanillyl-mandelic acid in a whole series of cases of tumours in children. The method used was one-dimensional paper chromatography (Käser, 1962). Some of our results were controlled by the procedure of high-voltage paper electrophoresis, and thanks are due to the collaboration of Dr. von Studnitz.

Our results are reported in Fig. 2: 25 neuroblastomas, all showed a significant rise in the urinary excretion of vanillyl-mandelic acid; three ganglioneuromas and seven malignant tumours not of neural origin, most of them Wilms' tumours,

FIG. 1.—The place of vanillyl-mandelic acid and of homovanillic acid in the metabolism of catecholamines.

showed normal excretion. Thus, this method allows us to establish the differential diagnosis between ganglioneuroma and neuroblastoma on the one hand, and neuroblastoma and other malignant tumours on the other hand (Käser and von Studnitz, 1961; Käser, 1961).

The differentiation of neuroblastoma from phaeochromocytoma, however, is *not* possible on this basis. Indeed, phaeochromocytomas also show an increase in urinary output of vanillyl-mandelic acid (Armstrong, McMillan and Shaw, 1957; von Studnitz and Hanson, 1959a, b; Sandler and Ruthven, 1959; Robinson, Ratcliffe and Smith, 1959; Gitlow, Mendlowitz, Khassis, Cohen and Sha, 1960; Ziegler, 1960; Sunderman, Cleveland, Law and Sunderman, 1960). Until recently, one could only use the clinical differential diagnosis and the classical hypertension tests (regitine, etc.). Now we hope to have found a means of establishing chemical diagnosis between the two tumours. Chromatograms of the urine from neuroblastoma cases all show not only a rise in vanillyl-mandelic acid, but also an enlargement of another phenolic acid spot which proved to be homovanillic acid (= 3-methoxy-4-hydroxyphenyl-acetic acid). This observation has recently been confirmed by von Studnitz (1961). This substance is a break-down product of dihydroxyphenylalanine (dopa) and of dopamin (Fig. 1), which are both normal metabolites leading to the synthesis of noradrenaline. From this point of view, we examined the urines of four phaeochromocytoma cases, kindly given us by other hospitals. We observed a normal output of homovanillic acid in all four cases, a fact which makes it possible to recognize chemically phaeochromocytoma from neuroblastoma.

Therefore, the quantitative determination of vanillyl-mandelic acid, and of homovanillic acid if phaeochromocytoma is suspected, seems to be a reliable test in establishing the diagnosis of sympathetic tumours.

The quantitative determination of vanillyl-mandelic acid is also valuable for the prognosis, and these determinations were done on six of our operated neuroblastoma cases for periods up to 18 months after operation. We could observe three different types of evolution as illustrated by the following three case notes.

Case Reports

Case 1. An 8-month-old boy suffered from a huge neuroblastoma sympatheticum located in the left lumbar fossa almost entirely surrounding the kidney. Total extirpation and nephrectomy were performed. Before the intervention, the urinary output of vanillyl-mandelic

FIG. 2.—Urinary excretion of vanillyl-mandelic acid (3-methoxy-4-hydroxy-mandelic acid) in 35 tumour cases in children.

Normal range =

● Neuroblastoma; ○ Ganglioneuroma; ▲ Other malignant tumours

acid was very high (Fig. 3). Subsequent controls showed that the excretion of vanillyl-mandelic acid immediately returned to normal. Eighteen months after surgery, the child is doing well and we are of the opinion that the cure will be lasting.

Case 2. A 3-month-old boy presented with a huge neuroblastoma of the right lumbar fossa. The extirpation was very difficult, as the tumour had infiltrated between vena cava, aorta and spine. Local lymph node metastases could only be partly removed. Subsequently, the output of vanillyl-mandelic acid (Fig. 4), which was very high before surgery, remained high, and a return to something like normal was only possible with complementary radiological treatment. It

FIG. 3.—Follow-up in Case 1.
(MHMA = 3-methoxy-4-hydroxy-mandelic acid = vanillyl-mandelic acid.)

FIG. 4.—Follow-up in Case 2.

FIG. 5.—Follow-up in Case 3.

is too soon to claim that this case is cured. Nevertheless, the tumour tissue, if still present, is chemically inactive.

Case 3. An 8-year-old boy suffered from a mediastinal tumour in the left paravertebral gutter. The tumour had been noticed when the child was 2 years old. He was sent to us only when the tumour began to increase. On operating, we found a well-encapsulated tumour at the inferior end, whilst a definite infiltration was seen at the superior end. Histologically the tumour was a ganglioneuroma at the lower pole and a neuroblastoma at the upper pole. Total extirpation was not possible. Postoperative treatment consisting of X rays and vitamin B₁₂ was unsuccessful. Very soon, clinical and radiological controls showed rapid proliferation of bone and brain metastases. The excretion rate of vanillyl-mandelic acid steadily increased until death occurred (Fig. 5).

Other observations of neuroblastomas show the same relation between tumour evolution and urinary excretion of vanillyl-mandelic acid. These observations led to the following conclusions: If the tumour has been radically extirpated, the output of vanillyl-mandelic acid returns immediately to normal values; if tumour tissue remains, the excretion of vanillyl-mandelic acid will remain high; if the tumour grows, or if metastases develop, the excretion of vanillyl-mandelic acid increases; if a patient with benign ganglioneuroma begins to have too much vanillyl-mandelic acid in his urine, one can surmise that the growth is degenerating into a neuroblastoma.

Summary

The quantitative determination of the urinary output of vanillyl-mandelic acid and of homovanillic acid was carried out in neural and other tumours in children. The excretion of vanillyl-

mandelic acid was always raised in cases of neuroblastoma and pheochromocytoma, but never in other tumours. The excretion of homovanillic acid was only increased in neuroblastoma, but not in pheochromocytoma. These determinations seem, therefore, to be a reliable laboratory test for the diagnosis of sympathetic tumours.

The rate of excretion of vanillyl-mandelic acid in neuroblastoma is directly related to the size of the tumour, and its determination is a good criterion in evaluating the follow-up after surgery or irradiation.

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