Section of Endocrinology

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Recent Advances in the Diagnosis of Endocrine Disease

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The Salivary Iodide Trap in Man: Clinical Applications

Iodide is concentrated not only in the thyroid gland but at other sites in the body including the salivary glands (Brown-Grant 1961). We should bear in mind five physiological facts about salivary iodide concentration:

(1) Significant quantities of iodide are secreted in saliva, the salivary clearance being of the same order as that by the thyroid and by the kidney (Table 1).

Table 1
Clearance of iodide (ml/min) by salivary glands, thyroid gland and kidney in normal subjects

	Mean	*SE*
Saliva:		
Resting	12·3	0·57
Fruit gum stimulation	25·2	0·85
Lemon juice stimulation	44·7	1·43
Thyroid	22·6	1·72
Renal	31·1	1·66

(2) The salivary iodine is almost entirely in the inorganic form even in conditions where organic iodine compounds are secreted in the urine (Papadopoulos *et al.* 1966, Alexander *et al.* 1966).
(3) The salivary iodide concentration is proportional to the plasma inorganic iodine concentration (PII) at physiological levels (Harden *et al.* 1966), and at PII concentrations of up to 100 µg/100 ml, i.e. about five hundred times the normal value (Harden, Alexander, Shimmins, Kostalas & Mason 1967). The linear relation in one subject is shown in Fig 1.
(4) The salivary iodide concentration is inversely related to flow rate: as the flow rate rises, the salivary iodide concentration falls. At parotid salivary flow rates greater than 1 ml/min, however, the concentration remains constant (Harden & Alexander 1967). The salivary iodide clearance nevertheless rises with increasing flow rate (Table 1).
(5) The iodide concentrating mechanisms in the thyroid and salivary glands are similar (Wolff & Maurey 1961), e.g. the iodide and perchlorate ions inhibit the concentration of iodide in the salivary and thyroid glands (Harden, Alexander, Shimmins, Kostalas & Mason 1968, Harden, Alexander, Shimmins & Robertson 1968).

What place do studies of the salivary iodide concentration have in clinical medicine?
Studies of iodide metabolism and kinetics: Significant quantities of iodide are secreted in saliva and, although this is normally all reabsorbed, the

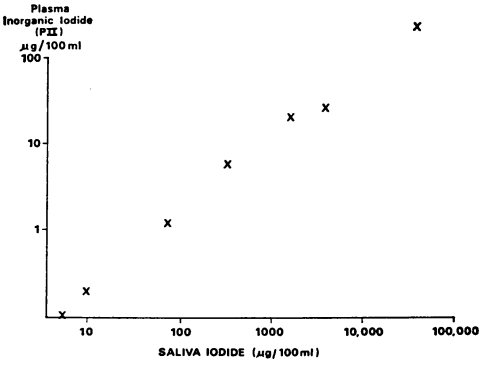

Fig 1 *Relationship in one subject between salivary iodide concentration and plasma inorganic iodine (PII) concentration*

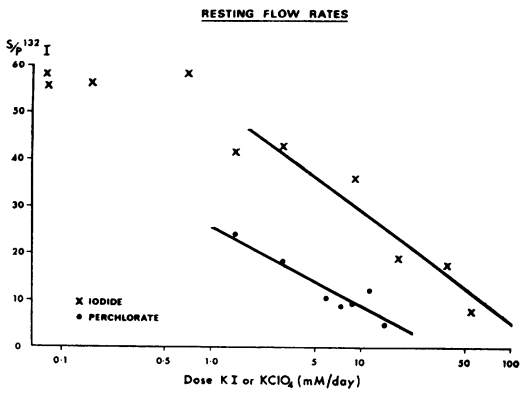

Fig 2 *Effect of administration of increasing doses of iodide and perchlorate on the saliva/plasma (S/P) ^{132}I ratio*

salivary iodide pool is important in some kinetic studies. Occasionally it may have practical implications. McCall *et al.* (1967) reported a patient in whom there was a discrepancy between the urinary ^{131}I excretion and the body ^{131}I retention 12 hours after administration of a tracer dose. This was found to be due to a loss of 24% of the ^{131}I dose in tobacco which he continuously chewed but never swallowed. Moreover, swelling of the salivary glands may occur following administration of iodide in cough mixtures or large therapeutic doses of radioiodine (Harden 1968).

Studies of the iodide trap: The iodide trap in the salivary glands can be studied more readily than the thyroid trap. Iodide secretion can be accurately measured in saliva and it is inorganic. In the thyroid gland, iodide which is trapped is organically bound and drugs which inhibit binding may also affect the trap. One can, for example, compare the inhibitory effect of the iodide and perchlorate ions on the iodide-concentrating mechanism (Fig 2). There is a linear negative relation between the saliva/plasma ^{132}I ratio and the logarithm of the dose of iodide and perchlorate. Higher doses of iodide are required to produce the same effect as perchlorate (Harden, Alexander, Shimmins & Robertson 1968).

Estimation of the plasma inorganic iodine (PII) concentration: Many aspects of iodine metabolism can be understood only if the PII is known. Iodide is present in the plasma in too small quantities to be measured directly. It is, however, concentrated in saliva and can be measured chemically. Therefore, following administration of a tracer dose, the specific activity of iodide in saliva is equal to the specific activity of iodide in plasma, i.e.,

$$\frac{\text{Plasma } ^{132}I}{\text{Plasma } ^{127}\text{iodide}} = \frac{\text{Saliva } ^{132}I}{\text{Saliva } ^{127}\text{iodide}}$$

therefore

$$\text{Plasma } ^{127}\text{iodide or PII} = \frac{\text{Saliva } ^{127}\text{iodide} \times \text{plasma } ^{132}I}{\text{Saliva } ^{132}I}$$

In normal subjects, the urine and the saliva techniques give similar results (Harden *et al.* 1965*b*). In thyrotoxicosis and in dyshormonogenesis, where there is organic iodine in the urine, falsely high PII values may be obtained (Alexander *et al.* 1966, Papadopoulos *et al.* 1966).

Diseases of the thyroid gland: Is estimation of the salivary iodide of any other value in thyroid disease? The salivary and thyroid traps are similar and in goitrous cretins with congenital inability of the thyroid to trap iodide the salivary glands are similarly affected (Stanbury & Chapman 1960, Wolff *et al.* 1964). The saliva/plasma iodide ratio is less than unity and this ratio may be used diagnostically where this type of dyshormonogenesis is suspected. We wondered whether minor defects of this type might be a factor in the ætiology of nontoxic goitre, but could not demonstrate them in patients with goitre and iodine deficiency, or in patients with goitre with a normal PII level (Harden, Chisholm, Shimmins & Alexander 1968). Koutras *et al.* (1967), on the other hand, claimed to find such differences in the salivary iodide trap in non-goitrous iodine-deficient subjects but the only difference demonstrated was a difference in salivary flow rate.

The saliva ^{131}I/plasma $PB^{131}I$ ratio has been suggested as a test of thyroid function (Thode *et al.* 1954, Maglione *et al.* 1966). In hyperthyroid patients, the thyroid uptake of radioactive iodine is high, and consequently the serum inorganic ^{131}I concentration low. The salivary ^{131}I concentration is proportional to the plasma level and is therefore also low (Table 2) (Harden *et al.* 1965*a*). The $PB^{131}I$ in thyrotoxicosis is high and therefore the ratio salivary ^{131}I/plasma $PB^{131}I$ is low. In hypothyroidism the ratio is high. But this ratio has little advantage over the $TP^{131}I/PB^{131}I$ ratio; indeed, the salivary ratio has

Table 2
Saliva ^{131}I/plasma $PB^{131}I$ ratio in hyper- and hypo-thyroidism

Thyroid state	*Thyroid ^{131}I uptake*	*Plasma inorganic ^{131}I*	*Saliva ^{131}I*	*Plasma $PB^{131}I$*	*Saliva ^{131}I/plasma $PB^{131}I$*
Hyperthyroidism	↑	↓	↓	↑	↓
Hypothyroidism	↓	↑	↑	N	↑

↑, increased; ↓, decreased; N, Normal

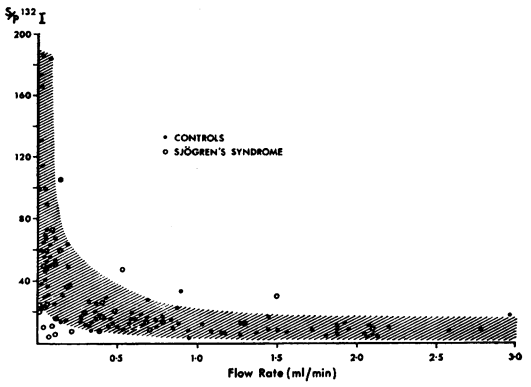

Fig 3 *Saliva/plasma ^{132}I ratios in normal subjects (shaded area) and in patients with Sjögren's syndrome*

the disadvantage that it will be altered by changes in salivary flow rate and in salivary iodide trapping. This test is too indirect and cannot be recommended for routine clinical diagnosis.

Diseases of the salivary gland: Tests of salivary gland function are at present unsatisfactory. We have looked to see if the saliva/plasma ^{132}I ratio might be abnormal in salivary gland disease (Mason *et al.* 1967). Some patients we studied with Sjögren's syndrome did have low values (Fig 3) and these were the patients with the most severe radiological changes noted on sialography.

Summary

Significant quantities of iodide are cleared from the plasma by the salivary glands. The iodine in saliva is almost entirely in the inorganic form. Its concentration varies with flow rate and the plasma inorganic iodine (PII) level. Estimation of the salivary iodide may be of value in studies of the iodide trap, in iodine kinetic studies, in estimation of the PII and diagnostically in goitrous cretins with congenital inability of the thyroid to trap iodide. The saliva $^{131}I/PB^{131}I$ ratio is a poor test of thyroid function. Further work is required to clarify the role of salivary iodide estimation and isotope scanning in salivary gland disease (Harden *et al.* 1967).

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A Critical Evaluation of the Tyrosine Tolerance Test in Thyroid Disease

Fasting plasma tyrosine levels are known to be raised in hyperthyroidism and lowered in hypothyroidism. Rivlin *et al.* (1965) found that the plasma tyrosine level half an hour after a tyrosine load was most helpful in the diagnosis of thyrotoxicosis, whereas Malamos *et al.* (1965), who only estimated fasting plasma tyrosine levels, found these to be higher than normal in all thyrotoxic patients studied. In neither study were the criteria for the selection of the control groups defined. In the validation of a test of thyroid function it is important to carry out the test in an unselected series of patients referred because of suspicion of the thyroid disorder. Patients who are found to be euthyroid by clinical assessment and by thyroid investigations other than that being validated can then be used as a control group for those found to be thyrotoxic. In this way patients with hyperthyroidism of all grades of severity are included and the test can be assessed in the clinical situation where it might subsequently be used.

Plasma tyrosine levels were estimated by the method of Waalkes & Udenfriend (1957). The oral tyrosine tolerance test was performed on an unselected consecutive group of patients referred to a medical outpatient clinic because hyperthyroidism was suspected. After an overnight fast a specimen of blood was obtained and the patient was given an oral dose of l-tyrosine (50 mg per kg body weight) suspended in 40 ml of water. Further blood samples were taken 30 and 60 minutes afterwards. Measurement of half- and one-hour plasma tyrosine levels was performed