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The interpretation of the serum protein-bound iodine: A review

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SYNOPSIS The effects of physiological and environmental factors, of thyroid and non-thyroid diseases, and of drugs on the serum protein-bound iodine are described and discussed.

The blood iodine consists of several fractions, not all of which are clinically important (Acland, 1958). The serum protein-bound iodine (PBI) is defined as that part of the total serum iodine which cannot be dialysed and is precipitated with the serum proteins. Physiological and pathological factors which may affect the serum PBI have been extensively reviewed (eg, Rall, Robbins, and Lewallen, 1964; Davis, 1966; Sandler and McGowan, 1967). The present review is concerned with the interpretation of the serum PBI in routine diagnosis.

Determination of the Serum PBI

The methods for determining serum PBI have been fully reviewed (Acland, 1958; Chaney, 1958; Henry, 1964, ch. 28; Robbins and Rall, 1967). The traditional normal range for the serum PBI in healthy adults is 4-8 μg/100 ml (Henry, 1964, p. 932). Investigators who use alkaline ashing techniques for determining serum PBI have reported lower limiting values, eg, 3·4-7·3 μg/100 ml (95% limits calculated from the data of Radcliff, Baker, Croydon, Hart, and Hales, 1964) and 3·5-7·5 μg/100 ml (Sisson, 1965). Workers using acid digestion techniques have reported wider normal ranges, eg, 3·6-8·8 μg/100 ml (Bodansky, Benua, and Penacchia, 1958) and 3·0-7·5 μg/100 ml (Wayne, Koutras, and Alexander, 1964—method of Farrell and Richmond, 1961). Michell (1966) reported that he had analysed 'about 500' sera with PBI values in the range 0·3-20·0 μg/100 ml both by the alkaline incineration method of Acland (1957) and by the Technicon PBI Auto-Analyzer (Technicon Instruments Ltd), which uses an acid digestion technique, and had found that the regression line of one method on the other did not differ significantly from the line of agreement. Contamination by iodine drugs is a serious problem in all methods for determining protein-bound iodine.

Iodothyronines in Serum

Thyroxine (T_4) makes up the greater part of the serum protein-bound iodine. The normal range for serum T_4 by column chromatography followed by alkaline ashing is quoted as 3·2-6·4 μg of T_4-I/100 ml (Henry, 1964, p. 950). Interference by some, but not all, iodine drugs is eliminated by this method (Henry, 1964, p. 950). Direct determination of T_4 in the column eluate after bromination (Pileggi and Kessler, 1968) gives results for T_4-I which are 0·13 μg/100 ml higher on average than the alkaline ashing technique. Priodax and Telepaque were found to interfere with the bromination method, but most radioopaque iodine drugs did not (Pileggi and Kessler, 1968). The normal 95% range for serum T_4 by the competitive protein-binding technique, converted to the same units, has been quoted as 2·6-7·2 μg of T_4-I/100 ml (Murphy and Pattee, 1966), 2·0-7·4 μg of T_4-I/100 ml (Cassidy, Benotti, and Peno, 1968), 2·6-6·9 μg of T_4-I/100 ml (Lucis, Cummings, Matthews, and Burry, 1969), and 2·9-7·5 μg of T_4-I/100 ml (Ekins, Williams, and Ellis, 1969). The use of competitive protein-binding methods avoids interference by iodine drugs (Murphy, 1969) but necessitates extraction of T_4 from serum with organic solvents, which may cause artefacts unless the solvent is evaporated above *p*H 9 (Bellabarba and Sterling, 1969).

The normal range (95% limits) for total serum 3:5:3′-tri-iodothyronine (T_3), calculated from the data of Nauman, Nauman, and Werner (1967), who used a competitive protein-binding technique, is

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0·11-0·28 μg of T_3-I/100 ml. The technique of Nauman *et al* (1967) has been criticized on the grounds that esterification artefacts could have been formed during extraction (Sterling, Bellabarba, Newman, and Brenner, 1969). A normal 95% range for total serum T_3 calculated from the data of Sterling *et al* (1969) is 0·10-0·16 μg of T_3-I/100 ml.

3:3′:5′:-Tri-iodothyronine and 3:3′-di-iodothyronine, although present in thyroid hydrolysates, are not normal serum constituents (Stanbury and Morris, 1957; Dunn and Stanbury, 1958).

Serum Proteins which Bind Thyroid Hormones

Nearly all the serum hormonal iodine (T_3 and T_4) in serum is bound to protein (Robbins and Rall, 1960). T_4 is attached under *in-vitro* conditions to several proteins, the most important of which are an α_2-glycoprotein, thyroxine-binding globulin (TBG), and a thyroxine-binding prealbumin (TBPA). In physiological conditions about 15% of the serum T_4 is bound to TBPA (Woeber and Ingbar, 1968). The remainder is largely bound to TBG with smaller amounts attached to albumin and certain lipoproteins (Robbins and Rall, 1952; Miyai, Itoh, Abe, and Kumahara, 1968). T_3 is bound more weakly than T_4 by TBG and is not bound at all by TBPA (Ingbar, 1960).

The unbound, or 'free', T_3 or T_4 may be estimated by determining the fraction of the serum T_3 or T_4 which has passed into the diffusate after dialysing the serum until equilibrium is attained (Oppenheimer, Squef, Surks, and Hauer, 1963; Ingbar, Braverman, Dawber, and Lee, 1965). In normal sera, on the average, 99·954% of the total T_4 is protein-bound (Sterling and Brenner, 1966) and 99·54% of the total T_3 is protein-bound (Nauman *et al*, 1967). These authors give normal ranges of 0·036-0·056% for the free T_4 fraction and 0·18-0·74% for the free T_3 fraction. It is important that the [^{131}I] T_4 or [^{131}I] T_3 used in the determination should not be contaminated by other iodothyronines (Volpert, Martinez, and Oppenheimer, 1967).

Serum Free T_3 and Free T_4

The normal range (95% limits) for the concentration of free T_4 in serum is 1·76-3·76 ng of T_4-I/100 ml or 35-74 pmoles/l (calculated from the data of Sterling and Brenner, 1966) and the normal range (95% limits) for serum free T_3 is 0·42-1·35 ng of T_3-I/100 ml or 11-35 pmoles/l (calculated from the data of Nauman *et al*, 1967). The upper limit of normal for the serum absolute T_3 level may be as low as 20 pmoles/l (Sterling *et al*, 1969).

Non-hormonal Iodine in the PBI

The PBI may contain iodoproteins, iodotyrosines, or inorganic iodide in addition to hormonal iodine. Contamination by iodine drugs is considered in a later section. The serum PBI is usually separated from free serum iodide by protein precipitation or by means of an anion-exchange resin. Thyroglobulin and iodoalbumin secreted by the thyroid gland (Robbins and Rall, 1960) and iodoalbumin secreted by the liver (Surks and Oppenheimer, 1969) remain in the protein fraction and are estimated as protein-bound iodine. Thyroglobulin is present only in minute traces in normal serum (Roitt and Torrigiani, 1967). Iodoalbumin from the liver could contribute up to 10 to 15% of the normal PBI (see Surks and Oppenheimer, 1969).

Free iodotyrosines are precipitated from serum in a zinc hydroxide precipitate but not to any significant extent in a trichloroacetic acid precipitate (O'Halloran and Wellby, 1966). If an anion exchange resin is used to remove inorganic iodide from serum, as in the case of the method used for the Technicon PBI AutoAnalyzer, iodotyrosines are included in the iodine remaining in the serum, which constitutes the 'total serum organic iodine', or TSOI (Austin and Koepke, 1966). Thus any iodotyrosines in serum are estimated as PBI if zinc hydroxide precipitation is used and as TSOI if iodide is removed from the serum by an anion exchange resin. Iodotyrosines are not found in the free state in normal sera (Wellby and O'Halloran, 1969) but are detectable in the serum in some thyroid diseases (see below). An exhaustive review of iodotyrosines in serum has been published (Rhodes, 1968). The evidence for the presence in serum of 'bound iodotyrosines', which may be identical with the serum iodoalbumin fraction of Surks and Oppenheimer (1969), has been summarized by Weinert, Masui, Radichevich, and Werner (1967).

Inorganic iodide is present in the PBI in significant quantities only if large doses of some organic iodine preparations (Chaney, 1958) or at least 1 g of inorganic iodide per day (Fisher, Oddie, and Epperson, 1965) have been administered.

Investigation of Anomalous Serum PBI Results

Serum PBI results which are at variance with the clinical assessment of thyroid state may be observed in any of the following situations: (1) if the serum TBG capacity is abnormal; (2) if iodinated drugs (including T_3 and T_4), or drugs which interfere with the analysis, have been administered; (3) if the thyroid gland is secreting a product of abnormal composition; and (4) if the peripheral metabolism

of thyroid hormone is abnormal. Ancillary methods of investigating the serum iodine are then necessary to supplement the serum PBI determination.

ABNORMALITIES IN SERUM TBG CAPACITY

These may be detected by comparing the absolute serum free T_4 level (Sterling and Brenner, 1966; Liewendahl and Lamberg, 1969) with the serum PBI, or more simply in routine practice by comparing the uptake by various absorbing agents of [^{131}I] T_3 added to serum (eg, Mitchell, Harden, and O'Rourke, 1960) with the serum protein-bound iodine. The T_3 uptake is a measure of unoccupied binding sites on TBG and is thus affected both by changes in TBG capacity and by changes in total serum T_4 (Goolden, Gartside, and Sanderson, 1967). Adsorption media in current use for T_3 uptake tests include resin, Sephadex (Hansen, 1966), charcoal coated with haemoglobin (Braverman, Foster, and Mead, 1967b), and charcoal coated with bovine serum albumin (Irvine and Standeven, 1967). The 'free T_4 index' or the 'free T_4 factor' (Clark and Horn, 1965; Goolden *et al*, 1967) may also be calculated from the T_3 uptake and the protein-bound iodine. The total serum T_4 is affected in the same way as the PBI by changes in TBG capacity. A free T_4 index based on the total T_4 and the resin uptake of [^{131}I] T_4 has been proposed (Howorth and Maclagan, 1969; Maclagan and Howorth, 1969).

Interference by drugs

Assessment of thyroid function in patients who have taken drugs which affect the serum PBI is best carried out after withdrawing the drug for a sufficient length of time to allow its effect to disappear. This is not always possible if the patient has received iodine-containing drugs whose contaminating effect on the serum PBI lasts for months or years (see below). In the presence of gross contamination of the PBI with organic iodine, the T_3 uptake is unaffected (Sisson, 1965) and measurements of total serum T_4 by protein binding (Murphy, Pattee, and Gold, 1966; Cassidy *et al*, 1968; Ekins *et al*, 1969) and of free T_4 by equilibrium dialysis (Sterling and Brenner, 1966) give accurate estimates of total and free serum hormonal iodine. Methods of determining free T_4 by adsorption of unbound T_4 onto Sephadex (eg, Liewendahl and Lamberg, 1969) are simpler than methods employing dialysis and are more suitable for routine use, but may be subject to artefacts during the adsorption stage which impair their accuracy (Hocman, 1966).

Abnormal serum iodoamino acids

The presence in serum of iodotyrosines or abnormal proportions of T_3 can be detected by semiquantitative chromatography of *n*-butanol extracts of the serum. Thin-layer chromatographic methods, of which several have been published (Taurog, 1963; West, Wayne, and Chavré, 1965; Sakurada, 1965 and 1966; Row, Volpé, and Ezrin, 1966; Coenegracht and Postmes, 1967; Favino, Emrich, and von zur Mühlen, 1967; Hoppe, Zappi, and Gries, 1967; Weinert *et al*, 1967; Fisher, 1968), appear to be the most sensitive but have not been proven in the routine laboratory. A method of separating T_3 from T_4 by gas-liquid chromatography has been described (Jaakonmäki and Stouffer, 1967), but the preparation of suitable derivatives of T_3 and T_4 appears to be too laborious for use in a routine laboratory. Solvent extraction of serum may cause artefacts because of esterification unless the solvent is evaporated in alkaline conditions (Bellabarba and Sterling, 1969).

Iodoproteins in serum

Thyroglobulin is not extracted from serum by *n*-butanol, and can only be demonstrated chromatographically if untreated serum is used (Tong, Taurog, and Chaikoff, 1952; Robbins, 1954). The soluble iodoprotein of the thyroid gland is soluble in *n*-butanol in the presence of trichloroacetic acid (Robbins, Rall, and Rawson, 1955), but its chromatographic properties are not known.

An increase in iodoproteins may be detected in serum (McConahey, Keating, Butt, and Owen, 1961) by observing an abnormally large difference (1 μg/100 ml) between the serum PBI and the serum butanol-extractable iodine (BEI) determined according to Man, Kydd, and Peters (1951). In practice, the difference between the PBI and the total T_4 measured by protein binding or by ion-exchange column (see above) would appear to be a more accurate estimate of non-T_4 iodine in the serum than the PBI-BEI difference. Iodinated contaminants are not distinguished from iodoproteins by the PBI-total T_4 difference.

The rate of peripheral metabolism of thyroid hormones

This is largely determined by the level of free T_4 in serum, and therefore depends not only on total T_4 but also on the binding capacity of TBG; however, other factors besides the TBG capacity may also be important (Oppenheimer, Surks, and Schwartz, 1969). Urinary losses of TBG and T_4 are important in the nephrotic syndrome (Rasmusson, 1956). Direct measurement of the rate of turnover of T_4, which is carried out by isotope studies *in vivo*, is not a routine procedure, and agreement has not yet been reached on the interpretation of the data from such studies (see Oppenheimer *et al*, 1969; Harland and Orr, 1969).

Serum PBI and the Clinical Assessment of Thyroid Function

Usually, in practice, the diagnosis of hypothyroidism or hyperthyroidism can be made on clinical grounds alone in 80-85% of patients presenting for the first time (Wayne, 1960). The requirement is then for a laboratory test to confirm the clinical diagnosis. Experience in thyroid clinics (Trotter, 1962; Wayne *et al*, 1964) seems to suggest that the best single confirmatory test for hypothyroidism is the serum PBI determination and the best single confirmatory test for hyperthyroidism is the thyroid ^{131}I uptake. Bender, Fitzgerald, and Williams (1968) recommended that the serum PBI, the thyroid ^{131}I uptake, and the resin uptake of [^{131}I] T_3 from serum should all be determined in a routine thyroid assessment. In the remaining 15-20% of cases considered by Wayne (1960), where there is diagnostic difficulty, a full thyroid investigation is necessary, but borderline or discrepant results may be obtained in all tests, including the serum PBI (Wayne *et al*, 1964; Thomson, Boyle, McGirr, MacDonald, Nicol, and Brown, 1968).

It is necessary to assess the thyroid state at regular intervals in treated thyrotoxic patients. Philp, Duthie, and Crooks (1968) used a combination of a clinical questionary, filled in by the patient's general practitioner, and of a serum PBI to screen patients for hypothyroidism. Barker and Bishop (1969) used for this purpose a combination of a postal symptomatic questionary, filled in by the patient, and a serum protein-bound iodine. In neither instance was the patient seen by a physician in the thyroid clinic unless the results of the questionary or the PBI determination suggested hypothyroidism. Both groups reported that there was no loss of efficiency in detecting hypothyroidism by combined questionary and serum PBI determination as compared with attendance at a thyroid clinic.

Variation of the Serum PBI with Age, Sex, and Ethnic Group

NEONATAL PERIOD AND INFANCY

The serum PBI of cord blood is above the normal adult level although below that of maternal blood (Rose, Russell, and Starr, 1963). A further increase occurs in the 12-24 hours after birth (Danowski, Johnston, Price, McKelvy, Stevenson, and McCluskey, 1951). The raised PBI in cord blood results from the high levels of TBG induced by foeto-placental oestrogen in the foetal blood (Dowling, Freinkel, and Ingbar, 1956a; Tervilä and Nordman, 1966). The postpartum increase is thought to be a physiological response to stress (Fisher, Oddie, and Burroughs, 1962; Fisher and Oddie, 1964). From the first week onwards, the serum PBI falls steadily until at 12 weeks most values lie within the normal adult range (Danowski *et al*, 1951). Occasional high results have been reported up to the age of 3 years (de Pascale, 1956).

Premature infants

In premature infants the postpartum rise tends to be smaller, slower in onset, and maintained for a longer time (Perry, Hodgman, and Starr, 1965).

Exchange transfusion

Exchange transfusion lowers the serum BEI for up to four days (Westphal and Man, 1962). The serum PBI would presumably show a similar fall.

CHILDHOOD AND ADOLESCENCE

Conflicting data have been published. Danowski, Huff, Erhard, Price, Brown, Wirth, and Stevenson (1952) reported a steady decrease with age up to 12-14 years followed by an increase up to adult levels. The changes were more marked in girls than in boys. Fisher, Oddie, and Wait (1964) reported low levels in postpubertal boys as compared with prepubertal boys and adults, but no changes with age in girls. Hart and McKendry (1967) confirmed the lack of variation with age in girls, but found an increasing trend in boys between 10 and 14 years. Goldsmith, Rauh, Kloth, and Dahlgren (1967) found no significant effect of sexual maturity on serum PBI in either sex.

It may be concluded that the normal changes in serum PBI with age in childhood and adolescence are unlikely to be clinically important.

OLD AGE

Conflicting data have been reported. Some results suggest that a small fall (0·3 μg/100 ml on average) occurs over the age of 50 years (Radcliff *et al*, 1964); other results suggest that no change occurs (Gaffney, Gregerman, Yiengst, and Shock, 1960; Valenti and Coscelli, 1966; Lederer and Bataille, 1969). One group reported an average increase of 1·5 μg/100 ml compared with young adults in a series of 14 senescent subjects (Scazziga, Lemarchand-Béraud, and Vannotti, 1964).

On balance, large serum PBI changes in old age seem unlikely to occur in the absence of thyroid disease or other conditions affecting the protein-bound iodine.

SEX DIFFERENCES IN SERUM PBI

Normal limits for the serum PBI in women were reported by Lowrey and Starr (1959) to be 0·3-0·4 μg/100 ml higher than the limits for men. This inves-

tigation was carried out before oral contraceptives came into wide use. The presence of a sex difference has not been confirmed in subsequent less extensive investigations (Radcliff *et al*, 1964; Braverman, Foster and Ingbar, 1967a).

MENOPAUSE

Serum PBI levels are within normal limits in patients complaining of menopausal symptoms (Manfredi, 1964).

PREGNANCY

High oestrogen levels induce an increase in the serum TBG capacity which causes a rise in serum PBI starting at about the third week and continuing until about a week after parturition (Heinemann, Johnson, and Man, 1948; Friis and Secher, 1955; Singh and Morton, 1956; Dowling *et al*, 1956a). It has been reported that serum PBI levels are 2-3 μg/100 ml higher in the last trimester than in the first two trimesters (Sisson, Marshall, Byall, and Capps, 1967).

Labour

An increase of 25% in the total T_4 of maternal serum occurs in the few hours before delivery, the change being reversed in the early puerperium (Siersbaek-Nielsen and Hansen, 1969). The resin uptake of [^{131}I] T_3 from serum follows a corresponding time course, increasing by 3% during labour and returning to its previous value immediately after delivery (Castron, Laakso, and Nikkari, 1969). The interpretation of these results is not clear.

Acute infection or weight gain in pregnancy

Each have been reported to be associated with a fall in serum BEI which could not be explained by changes in T_4-binding capacity (Man, Reid, and Jones, 1968).

Threatened abortion

Agreement has not been reached on the question whether a low serum PBI in pregnancy is a sign of threatened abortion (Magnin, Bigot, Nuon-Hoa, and Moine, 1968).

ETHNIC VARIATIONS IN THE SERUM PBI

Serum PBI levels within the limits for Caucasian adults have been reported in Japanese, Koreans, Okinawans, and Guamese (Burdick and Brown, 1968), in adult negroes (Starr and Nicoloff, 1967), and in Xavante Indians (Neel, Mikkelson, Rucknagel, Weinstein, Goyer, and Abadie, 1968). Negro preadolescent children have been reported to have serum PBI levels averaging 0·8 μg/100 ml higher than Caucasian preadolescent children as a result of a higher serum TBG capacity in the negro children (Starr and Nicoloff, 1967).

In the Eskimo, upper and lower limits for the serum PBI are 1 μg/100 ml above those for Caucasians (Gottschalk and Riggs, 1952; Davies and Hanson, 1965), and in Marshall Islanders the serum PBI level averages 2 μg/100 ml above that of Caucasians, probably because an abnormal iodoprotein is present in the blood (Rall and Conard, 1966).

Effect of Climatic and Seasonal Changes on the Serum PBI

HOT CLIMATIC CONDITIONS

The serum PBI has been consistently reported to be low in hot weather compared with the serum PBI levels of the same subjects in temperate weather (Thompson and Kight, 1963; Watanabe, Uematsu, and Horii, 1963; Duruisseau, 1965). Although haemoconcentration is known to occur in colder weather (Wilson, 1966), the haematocrit changes in the subjects studied by Thompson and Kight (1963) and by Watanabe *et al* (1963) were insufficient to account for the variations in serum PBI which they observed.

COLD CLIMATIC CONDITIONS

Reports on the effect of cold weather on the serum PBI are inconsistent. Falls have been recorded by Ingbar and Bass (1957) and by Watanabe *et al* (1963). Gottschalk and Riggs (1952) reported that the serum PBI was unaffected by life in the Arctic. Duruisseau (1965) found that the serum PBI of subjects living in Montreal was highest in the winter

Acute exposure to cold

Cold affects the serum PBI only insofar as it causes haemoconcentration (Wilson, 1966; Berg, Utiger, Schalch, and Reichlin, 1966; Suzuki, Tonoue, Matsuzaki, and Yamamoto, 1967).

Acclimatization to cold weather

In the Antarctic this has been reported to be associated with a rise in serum PBI to normal or high levels from the low values observed during the first week of exposure (Staquet, 1965).

SIZE OF THE THERMAL EFFECTS ON THE SERUM PBI

When thermal effects occurred, the differences between the maximum and minimum serum PBI levels in different climatic conditions reported by the authors quoted were as much as 2 μg/100 ml.

CLIMATIC STRESS AND THE SERUM PBI

It is possible that the degree of climatic stress may determine whether the serum PBI will fall during a particular season of the year. The climatic conditions (severe heat and severe cold) found to be associated with low serum PBI levels by Watanabe *et al* (1963) had previously been reported to be associated with a reduction in the count of circulating eosinophils (Watanabe, Aoki, and Nagai, 1956). This suggests that the climatic stress was sufficient to increase the output of adrenal corticosteroids in the subjects studied. Corticosteroids are known to reduce the serum PBI as a result of reduced TSH secretion and increased peripheral utilization of T_4, as well as by haemodilution (Ingbar and Freinkel, 1956; Danowski, Moses, and Mateer, 1962; Blomstedt and Einhorn, 1965 and 1967).

HIGH ALTITUDE AND LOW ATMOSPHERIC PRESSURE

The adaptation to life on a mountain or the experimental exposure of subjects to low pressure in a pressure chamber increases the serum PBI (or BEI) by 1-2 μg/100 ml (Surks, 1966; Siri, van Dyke, Winchell, Pollycove, Parker, and Cleveland, 1966; Surks, Beckwitt, and Chidsey, 1967; Schmidt-Kessen, 1967). The serum TBG capacity is increased but the serum free T_4 is also increased (Surks, 1966; Surks *et al*, 1967), so it would appear that the physiological activity of the thyroid gland is increased. The physiological mechanism underlying these changes has not been elucidated but the low oxygen tension is presumably the stimulus.

Effects of Stress on the Serum PBI

It was thought for some time that all forms of physical and emotional stress were without effect on the serum PBI (Volpé, Vale, and Johnston, 1960). This conclusion appears to be incorrect, since climatic stress severe enough to cause increased adrenocortical activity is associated with a fall in serum PBI (see previous section). It is important to exclude haemoconcentration or haemodilution in response to a stressful environmental stimulus as a cause of any changes in the serum PBI concentration which may be observed.

PHYSICAL STRESS

Muscular exercise

This is without effect on the serum PBI although it increases the rate of T_4 secretion and degradation (Irvine, 1968).

Electroconvulsant therapy

This is associated with a transient increase of 0·5 μg/100 ml in serum PBI within the first hour followed by a fall to a level 0·5 μg/100 ml below the original value, maintained between eight and 24 hours after therapy; changes in plasma volume account completely for these variations in the serum PBI (Reichlin and O'Neal, 1962).

Surgical intervention

Surgery has no effect on the serum PBI (Volpé *et al*, 1960).

EMOTIONAL STRESS

Tingley, Morris, Hill, and Pittman (1965) reported that emotional stress in students caused an increase of 0·5 μg/100 ml in the serum protein-bound iodine. Levi (1967) subjected a group of individuals to a severe experimental psychological stress situation which was continuous for three days, and found that 30 out of 31 subjects showed increases in serum PBI ranging from 0·5 to 5·8 μg/100 ml. No significant changes occurred in the haematocrit. It is interesting that emotional stress should cause an increase in serum PBI whereas severe climatic stress should cause a fall, presumably associated with adrenocortical hyperactivity. Levi (1967) did not report any measurements of TBG capacity or other indices of thyroid function in his subjects. It is possibly significant that in 29 of his 31 subjects the erythrocyte sedimentation rate increased by between 1 and 12 mm/hr after exposure to the stress situation. The mechanism by which severe emotional stress may increase the serum PBI requires further investigation.

Diurnal Variations in Serum PBI

Diurnal variations in the serum PBI level are often discounted as being clinically unimportant, eg, by Davis (1966). Nevertheless, Margolese and Golub (1957) in a careful study observed daily fluctuations of as much as 1·5 μg/100 ml in the serum PBI level of individual subjects. There was evidence of autocorrelation indicating that non-random oscillatory changes in the serum PBI were occurring in a definite diurnal rhythm. Serum PBI levels were more variable in women than in men, higher values and greater scatter occurring in the luteal phase of the menstrual cycle. The mechanism of these diurnal changes is not known.

Dietary and Other Environmental Effects on the Serum PBI

ABSORPTION OF IODINE OR IODIDE AFTER ENVIRONMENTAL EXPOSURE

Oral iodide

Oral administration of iodide has little effect on the serum PBI until the intake reaches 1 g per day, when

the serum PBI level may increase by 0·7 μg/100 ml (Fisher *et al*, 1965). A diet containing a high proportion of seaweed causes iodide goitre (qv) to develop, with a high or normal PBI and a low serum T_4 (Suzuki, Higuchi, Sawa, Ohtaki, and Horiuchi, 1965).

Proprietary foods
Some proprietary invalid or baby foods contain iodide which may cause increases in serum PBI, eg, Metrecal, which may be responsible for a rise of 1 to 3 μg/100 ml (Steinberg and Leifheit, 1965).

Schiller's test
Vaginal application of iodine and potassium iodide in Schiller's test for detecting carcinoma of the cervix does not affect the serum PBI (Braverman, Perkins, Regnante, and Coté, 1968).

Iodinated water
Swimming in iodinated water has little effect on the serum PBI until the concentration in the water reaches 5 mg/l when an average increase of 1·3 μg/100 ml in the serum PBI has been observed (Freund, Thomas, Bird, Kinman, and Black, 1966).

Atmospheric exposure
Atmospheric exposure to iodine in laundry workers resulting from the use of iodophor detergents has no effect on the serum PBI (Vought, London and Brown, 1964).

DIETARY GOITROGENS
Several edible plants, particularly in the Brassica family, contain goitrogens, either thiocyanates or thiouracil-like compounds, which may play a subsidiary part in the aetiology of endemic iodine-deficiency goitre (Kilpatrick and Wilson, 1964).

Milk substitutes containing soya bean are strongly goitrogenic in some infants (Rawson and Rall, 1955; van Wyck, Arnold, Wynn, and Pepper, 1959; Shepard, Pyne, Kirschvink, and McLean, 1960). It is possible that these infants are particularly sensitive to a goitrogen in soya bean which may interfere with T_4 absorption (Pinchera, MacGillivray, Crawford, and Freeman, 1965a).

EFFECT OF FLUORIDE ON THE SERUM PBI
Fluoridation of the water supply does not affect the serum PBI (Leone, Leatherwood, Petrie, and Lieberman, 1964; Ritzel and Hertzog, 1965).

Massive doses of fluoride (5-10 mg per day for several weeks) are goitrogenic (Galletti and Joyet, 1958).

Fluoride does not interfere with the analysis of serum PBI (Hallman, Bondy, and Hagewood, 1951).

Effect of Posture on the Serum PBI

Recumbency for one and a half hours causes an average decrease of about 0·8 μg/100 ml in the serum PBI as compared with the levels in the ambulant subjects, because of haemodilution (Smeenk and van den Brand, 1965). This should be borne in mind when comparing results from outpatients with those from patients in bed in hospital.

Blood Collection and Preparation of the Patient

PREVENTION OF CONTAMINATION OF THE SAMPLE
Disinfectants containing iodine or mercurials should not be used to prepare the skin for a venepuncture.

Blood should preferably be collected into disposable plastic syringes and containers.

INTRAVENOUS INFUSION
The use of one type of plastic tubing (Bard Intracath) in intravenous infusion has been found to cause artefactually raised serum PBI values as a result of an aliphatic iodine compound being washed out of the tubing and becoming protein bound in the serum (Simbari and Houghton, 1969).

EFFECT OF VENOUS OCCLUSION
Occlusion of the veins for five minutes before venepuncture was found to increase the serum PBI by 1·35 μg/100 ml on average (Lewitus and Steinitz, 1963). Samples of blood for serum PBI determinations are best taken without venous occlusion.

Diagnostic Limits for the Serum PBI

Suggested normal clinical ranges for different Caucasian population groups are given in Table I.

Age	*Premature*			*Full Term*
	Weight (kg)			
	1-1·5	*1·5-2*	*2-2·5*	*>2·5*
	Normal Range for Serum PBI (μg/100 ml)			
Cord blood	4- 7·5	4- 8	5 - 9	5 -10
1st week	5-11·5	4-16	6 -16	8 -16
2nd week	3-11	5-12	6·5-11·5	4·5-10·5

Table Ia *Ranges for serum PBI in neonates*

Prepubertal Children	*Normal Range for Serum PBI (μg/100 ml)*
3 w-3 mth	4-10·5
3 mth-5 yr	4- 8·5
5 yr-puberty	4- 7

Table Ib *Ranges for children*[1]

Postpubertal Girls and Women	*Normal Range for Serum PBI (μg/100 ml)*
Not pregnant (not on oral contraceptives)	4 - 8
Pregnant (3rd week to end of 2nd trimester)	4·5-11·5
Pregnant (3rd trimester to 1 week postpartum)	7·5-13·5
Not pregnant on oestrogenic oral contraceptives	4·5-13·5

Table Ic *Ranges for girls and women*[1,2,3]

Postpubertal Boys and Men	*Normal Range for Serum PBI (μg/100 ml)*
Up to 18 years	3·5-6·5
Over 18 years	3·5-7·5

Table Id *Ranges for boys and men*[1,2]

[1]Diurnal variations (Margolese and Golub, 1957) are ignored. It is recommended that samples for PBI should be taken at one time of day (preferably 9.0 am).
[2]It is recommended that lower limits should be reduced by 0·5 μg/100 ml and upper limits by 1 μg/100 ml to compensate for postural effects (Smeenk and van den Brand, 1965) in hospital patients in bed.
[3]Ekins *et al* (1969) reported that there was no significant difference between the range of serum total T_4 in pregnant subjects and in non-pregnant subjects on oral contraceptives. The serum PBI range in pregnancy is therefore suggested for patients on oral contraceptives.

They have been arrived at after a consideration of the work of Danowski *et al* (1951), de Pascale (1956), Singh and Morton (1956), Margolese and Golub (1957), Lowrey and Starr (1959), Rose *et al* (1963), Radcliff *et al* (1964), Fisher *et al* (1964), Perry *et al* (1965), Smeenk and van den Brand (1965), Sisson *et al* (1967), and Ekins *et al* (1969).

Serum PBI in Thyroid Diseases

SIMPLE GOITRE

This condition results from iodine deficiency or from the presence of goitrogens in the diet. The pathological changes in the thyroid gland are caused by increased secretion of TSH in response to a reduced output of thyroid hormone. The natural history of simple goitre is progressive (Taylor, 1953). In its later stages the disease is often called 'nodular' goitre. The term 'sporadic' goitre is used to describe cases of simple goitre which appear in a population whose iodine intake is normal, whereas the term 'endemic' goitre refers to simple goitre which occurs in a large proportion of a population whose iodine intake is low. Patients suffering from iodine-deficiency goitre are characteristically euthyroid, and the hypothyroidism or hyperthyroidism which occur rarely in such patients are independent of the endemic goitre (Wayne *et al*, 1964; Matovinović and Ramalingaswami, 1960; Clements, 1960).

In endemic goitre, most serum PBI levels are at the lower end of the normal range, but there is a wide scatter of values including some very low and some very high results (Ramalingaswami, 1964; Buttfield, Black, Hoffman, Mason, Wellby, Good, and Hetzel, 1966). Low serum PBI levels are often not associated with clinical hypothyroidism (Ramalingaswami, 1964), suggesting that physiological adaptation may occur to the low iodine intake. The secretion of a higher proportion of T_3 by the thyroid gland, demonstrated by de Visscher, Beckers, van den Schriek, de Smet, Ermans, Galperin, and Bastenie (1961) and Parra Jiménez, García, Roche, and Gaede (1962), would conserve iodine and might explain the discrepant values. It is also possible that malnutrition and consequent hypoproteinaemia, which may be present in many endemic goitrous areas, could reduce the serum TBG capacity.

High serum PBI levels may be associated with the presence of a solitary hyperfunctioning nodule, the so-called 'toxic adenoma', which has an indeterminate natural history (Silverstein, Burke, and Cogan, 1967; Horst, Rösler, Schneider, and Labhart, 1967). In one patient, after haemorrhage into a colloid nodule, the serum PBI was found to be raised either as a result of the release of thyroid iodine or because thyrotoxicosis was already present and precipitated the haemorrhage (Greenberg, 1966).

About 10% of patients with simple goitre have been reported to have an increased PBI-BEI difference, suggesting the presence of iodotyrosines or abnormal serum iodoproteins in simple goitre (McConahey *et al*, 1961).

FAMILIAL GOITRE WITH DYSHORMONOGENESIS

From time to time cases of goitre showing a marked familial incidence have been described. Further study showed that these patients' condition could be ascribed to deficiencies in enzymes required for the synthesis of thyroid hormone (see accounts by Wolff, Thompson, and Robbins, 1964; Murray and McGirr, 1964; Lissitzky, Codaccioni, Cartouzou, and Mante, 1964; Klevit, Eberlein, and Bongiovanni, 1965; Bax, 1966; Lizarralde, Jones, Seal, and Jones, 1966; Lissitzky, Codaccioni, Bismuth, and Depieds, 1967).

The protein molecule of thyroglobulin is synthesized first and is subsequently iodinated in several stages (see Pastan, 1966; Pitt-Rivers, 1967). Iodide is first concentrated in the gland by an active transport mechanism, the 'iodide trap'. Iodide is then oxidized by the thyroid peroxidase and combines with the enzyme to form 'active iodine', which iodinates tyrosine residues in thyroglobulin to MIT and DIT residues (see Nunez and Pommier, 1968). Two iodotyrosine residues are finally coupled together to form an iodothyronine residue in thyro-

globulin. Thyroglobulin is stored in the thyroid follicles and hormonal iodine (T_3 and T_4) is released by subsequent hydrolysis of thyroglobulin. DIT and MIT, which are also released by hydrolysis of thyroglobulin, are rapidly deiodinated by the thyroid dehalogenase, and their iodine is returned to the intrathyroidal iodide pool.

The enzyme defect which causes familial goitre may occur at any of the stages of hormone synthesis. Clinically, the patients are always goitrous and may show additional familial disorders, eg, deaf mutism in Pendred's syndrome, and they may be either euthyroid or hypothyroid (see references quoted above).

TARGET ORGAN REFRACTORINESS

A familial syndrome, including goitre, deaf mutism, and stippled epiphyses, has been reported in which a high serum PBI and T_4 were attributed to target-organ refractoriness (Refetoff, de Wind, and de Groot, 1967).

IODIDE GOITRE

Long-continued administration of iodide, iodine-containing foods, or drugs which are metabolized to iodide may cause myxoedema and goitre in susceptible individuals, with a normal or high serum PBI and low serum T_4 levels (see review by Wolff, 1969). Wolff (1969) considered that the high serum PBI level resulted from iodide contamination, but Danowski, Johnston, and Greenman (1950) found that the serum PBI level remained raised after ceasing iodide administration when the plasma inorganic iodide had returned to normal. These findings suggested that iodide caused an increase in serum PBI due to the formation of iodoproteins.

HYPOTHYROIDISM

Clinical aspects of hypothyroidism are discussed in standard texts (eg, Trotter, 1962; Means, de Groot, and Stanbury, 1963; Wayne *et al*, 1964). The serum PBI tends to be low in all types of hypothyroidism, whether primary or secondary to hypopituitarism, except in some forms of thyroid dyshormonogenesis (Werner, Block, Mandl, and Kassenaar, 1957) and in iodide goitre (see above), when the serum PBI may be normal or high because iodotyrosines or iodoproteins in the serum are estimated as protein-bound iodine. There is not much overlap between the serum PBI ranges for hypothyroid and euthyroid subjects. Radcliff *et al* (1964) found that about 2% of 37 hypothyroid patients had a serum PBI above 3·4 μg/100 ml and about 2% of 311 euthyroid subjects had a serum PBI below 3·4 μg/100 ml (lowest 2·7 μg/100 ml). Bender *et al* (1968) found no hypothyroid patients out of 50 with a serum PBI above 3·7 μg/100 ml, and about 7% of 724 euthyroid patients with a serum PBI below 3·8 μg/100 ml (lowest 2·3 μg/100 ml).

HYPERTHYROIDISM

Clinical hyperthyroidism (see Trotter, 1962; Means *et al*, 1963; Wayne *et al*, 1964) is a feature of Graves' disease (diffuse toxic goitre) and toxic nodular goitre, and may occur in association with a solitary thyroid adenoma, with De Quervain's thyroiditis, with Hashimoto's thyroiditis, and in thyroid addiction, and also be associated with a dermoid cyst and struma ovarii (Perlmutter and Mufson, 1951).

Different authors have reported a different degree of overlap between the serum PBI ranges in hyperthyroid and euthyroid subjects. Wayne *et al* (1964, p. 176) found serum PBI levels ranging from 4 to 21·6 μg/100 ml in 40 clinically hyperthyroid patients, compared with their normal range of 3 to 7·5 μg, 100 ml; Radcliff *et al* (1964) found PBI levels between 5·5 and 16·25 μg/100 ml in 41 clinically hyperthyroid patients, compared with their normal range of 3·4 to 7·3 μg/100 ml. On the other hand, Bender *et al* (1968) found only four out of 115 hyperthyroid patients with serum PBI levels below 8·4 μg/100 ml but 83 out of 724 euthyroid patients with serum PBI levels between 8·0 and 12·8 μg/100 ml. Clinical experience seems to indicate that the serum PBI does not usually discriminate between hyperthyroid and euthyroid subjects as well as the thyroid ^{131}I uptake, although the latter test is less reliable than the serum PBI when the intrathyroidal or extrathyroidal iodine pools are abnormal in size (Wayne *et al*, 1964, p. 224).

GRAVES' DISEASE (THYROTOXICOSIS)

Characteristically, patients suffering from Graves' disease show a diffuse goitre and hyperthyroidism, with or without infiltrative orbitopathy, and they often have high levels of the long-acting thyroid stimulator (LATS) in the serum (Major and Munro, 1962; Wayne *et al*, 1964; Pinchera, Pinchera, and Stanbury, 1965b). The severity of the exophthalmos does not appear to be related to the serum level of LATS (Major and Munro, 1962; Pinchera, Pinchera, and Stanbury, 1965b). A few patients with progressive exophthalmos and high serum levels of LATS, who are thus presumed to have active Graves' disease, may be euthyroid or hypothyroid as a result of a low thyroid reserve (Liddle, Heyssel, and McKenzie, 1965). Thyroid acropachy may occur in untreated thyrotoxic patients or in thyrotoxic patients rendered euthyroid or hypothyroid by treatment (Gimlette, 1960; Kinsella and Back, 1968). It is associated with high serum levels of LATS (Pinchera *et al*, 1965b).

INFECTIVE THYROIDITIS

The diagnosis of this rare condition is made on clinical grounds without recourse to the serum PBI (Hendrick, 1956). Temporary hypothyroidism may follow medical or surgical treatment (Hendrick, 1956). A normal serum PBI has been reported in one case at the time of surgery (Richie, 1959).

SUBACUTE GRANULOMATOUS (DE QUERVAIN'S) THYROIDITIS

De Quervain's thyroiditis is a chronic inflammatory condition of unknown, possibly viral, aetiology (see Czerniak and Harell-Steinberg, 1957; Trotter, 1962; Hintze, Fortelius, and Railo, 1964; Skillern, 1964; Wayne *et al*, 1964). In the early stages, a raised serum PBI level is associated with a depressed thyroid ^{131}I uptake. The high serum PBI level is sometimes caused by the presence of an abnormal serum iodoprotein (Ingbar and Freinkel, 1958), but a high serum T_4 level and frank thyrotoxicosis may be present. In later phases, low or low normal serum PBI levels may be observed.

HASHIMOTO'S THYROIDITIS AND FOCAL LYMPHOCYTIC THYROIDITIS

Both these diseases are associated with the presence of antithyroid antibodies in the serum and thus appear to have an autoimmune aetiology (see Means *et al*, 1963; Paine, Terplan, Rose, Witebsky, and Egan, 1957). Lymphocytic thyroiditis is distinguished from Hashimoto's disease by the type of lymphocytic infiltration, which appears in discrete foci in the former but is diffuse in the latter, and by the absence in lymphocytic thyroiditis of the Askanazy cells which are typical of Hashimoto's disease (Williams and Doniach, 1962).

In Hashimoto's disease, the patients may present in hyperthyroid, euthyroid, or hypothyroid states (Means *et al*, 1963). In the active phase, thyroglobulin in the serum may cause elevations of the serum PBI (Owen and McConahey, 1956; McConahey *et al*, 1961). In the fibrous variant of Hashimoto's disease the lymphocytic and fibrous infiltration of the thyroid gland is marked, and low serum PBI levels are found from the beginning (Beierwaltes, 1965). Hashimoto's thyroiditis has a well known association with collagen diseases (Means *et al*, 1963).

In focal lymphocytic thyroiditis the serum PBI is variable (Gribetz, Talbot, and Crawford, 1954).

RIEDEL'S STRUMA

This rare disease is an invasive fibrous thyroiditis characterized by dense fibrous adhesions extending into the tissues of the neck around the thyroid. Woolner, McConahey, and Beahrs (1957) observed five hypothyroid patients in a series of 20 suffering from Riedel's struma, the rest being euthyroid.

NEOPLASMS OF THE THYROID GLAND

Patients with thyroid neoplasms are usually euthyroid. Lindsay (1960, p. 27) reported a 2% incidence of hyperthyroidism and a 4% incidence of hypothyroidism in a series of 293 patients with thyroid cancer. Raised serum PBI levels associated with thyroid tumours usually result from the presence of iodoproteins in serum (Robbins *et al*, 1955). Mack, Hart, Druet, and Bauer (1961) described a patient with a thyroid tumour which was shown by chromatographic examination of the serum to secrete mainly T_3. They reported that after radiotherapy the proportion of T_4 to T_3 reverted to normal.

ABNORMALITIES OF THE SERUM IODINE IN THYROID DISEASES

Iodotyrosines may form the major serum iodine component in certain types of thyroid dyshormonogenesis (Werner *et al*, 1957). Significant amounts of iodotyrosines (up to 10% of the total serum iodine) have been reported to be present in the sera of 78 out of 128 thyrotoxic patients (Farran, Lea, Goolden, and Abbott, 1959; Shalom, 1966; Földes, Gyertyánfy, Tamás, Gesztesi, and Takács, 1967; Wellby and O'Halloran, 1969).

A high ratio of T_3 to T_4 in the serum has been reported in five out of nine patients with endemic goitre (de Visscher *et al*, 1961) and the observation was confirmed by Parra Jiménez *et al* (1962). High serum T_3 levels have been reported in individual patients suffering from some types of thyroid dyshormonogenesis (Rupp, Chavarria, Paschkis, and Chublarian, 1959; Werner, Row, and Radichevich, 1960; Lissitzky *et al*, 1967), from a toxic thyroid adenoma (Shimaoka, 1963), from thyrotoxicosis (Rupp and Paschkis, 1961), and from thyroid carcinoma (Mack *et al*, 1961).

Abnormal amounts of iodoproteins, either thyroglobulin or an iodoalbumin, have been found in the serum in association with simple goitre (Brown, Lowenstein, Greenspan, and Mangum, 1966), with some autonomous thyroid nodules (Kahn, Cogan, and Berger, 1962), in some types of thyroid dyshormonogenesis (de Groot and Stanbury, 1959; Dowling, Ingbar, and Freinkel, 1961; Lissitzky *et al*, 1964), after iodide administration (Danowski *et al*, 1950), in thyrotoxicosis after therapeutic doses of radioiodine (Cameron and Fletcher, 1959; Owen, McConahey, Childs, and McKenzie, 1960; Cavalieri, 1961; Stanbury and Janssen, 1962), in De Quervain's thyroiditis (Ingbar and Freinkel, 1958), in Hashi-

moto's thyroiditis (Owen and McConahey, 1956), and in thyroid carcinoma (Robbins *et al*, 1955).

Effect of Non-thyroid Diseases on the Serum PBI

Euthyroid patients suffering from non-thyroid diseases may have serum PBI levels outside the normal range as a result of (1) changes in the serum TBG capacity, eg, in acute intermittent porphyria (Hollander, Scott, Tschudy, Perlroth, Waxman, and Sterling, 1967b), or (2) a combination of a reduced serum TBG capacity and urinary losses of T_4 and TBG, eg, in the nephrotic syndrome (Rasmusson, 1956). Increased faecal losses of T_4 in active pancreatic steatorrhoea do not reduce the serum PBI level (Hiss and Dowling, 1962) and are probably unimportant clinically except in the case of goitrogenic soya bean preparations, which are thought to contain a factor which interferes specifically with T_4 absorption in susceptible subjects (Pinchera *et al*, 1965a).

In addition, abnormal serum PBI levels in non-thyroid disease may be observed because the rate of secretion of TSH by the pituitary has been affected, because the non-thyroid disease has an association with thyroid disease, or because the non-thyroid disease is a manifestation of a disorder of the thyroid gland.

In many cases of non-thyroid diseases discrepancies may arise between the clinical thyroid state and the serum free T_4 level because of abnormalities in the tissue binding and metabolism of T_4 (Oppenheimer, 1968; Oppenheimer *et al*, 1969). The influence of these changes in peripheral T_4 metabolism in non-thyroid disease on the serum PBI level has not yet been fully assessed.

GENETIC AND DEVELOPMENTAL DISORDERS

The level of serum TBG is genetically determined, and rare cases of congenitally reduced or absent TBG (Ingbar, 1961a; Refetoff and Selenkow, 1966; Nikolai and Seal, 1967; Kraemer and Wiswell, 1968) and congenitally increased TBG (Beierwaltes and Robbins, 1959; Jones and Seal, 1967) have been reported. Euthyroid subjects with a low serum TBG have low serum PBI levels and those with a high serum TBG have a high serum PBI level. A high serum PBI level has been reported in a case of Fanconi's anaemia (London, Drukker, and Sandbank, 1965) and a high TBG capacity in a case of hereditary anhidrotic ectodermal dysplasia (Hippe, 1967), but these associations may have been coincidental.

The determination of the serum PBI has been extensively used to investigate thyroid function in developmental disorders, but abnormal values are rare. One case of a mosaic XO/XY/XXY genotype was reported in association with a defect in thyroglobulin synthesis, a normal serum PBI level, and a low serum T_4 (Lizarralde *et al*, 1966), and one out of four cases of De Lange's syndrome had a low serum PBI, the serum PBI being normal in the other three (Hillman, Hammond, Noé, and Reiss, 1968).

Proven cases of clinical hypothyroidism or hyperthyroidism are extremely rare in mongolism (Hayles, Hinrichs, and Tauxe, 1965). The serum PBI (Fisher *et al*, 1964; Marks and Hamlin, 1967), TBG capacity (Rimoin, 1965) and free T_4 (Marks and Hamlin, 1967) in mongols have been reported not to differ significantly from the values in non-mongol control subjects. On the other hand, Dodge, Neill, and Scally (1967) recorded a high proportion of low serum PBI and BEI levels with high PBI-BEI differences in mongols, although they did not report any determinations on control subjects, and Fisher *et al* (1964) found that the T_3 resin uptake was significantly higher on average in mongols than in control subjects. These last results might suggest that abnormal TBG or iodoprotein was present in the serum of some mongols, but methodological explanations for the abnormal findings cannot be excluded. Pearse, Reiss, and Suwalski (1963) reported low thyroid ^{131}I uptakes in 17 out of 125 male and seven out of 26 female mongols, and a high uptake in one patient. They also stated that diffuse or nodular thyroid enlargements were noted in many of their patients. An association between mongolism and thyroid dyshormonogenesis cannot thus be excluded.

The differentiation of cretins from mongols, from rachitic and chondroplastic dwarfs, from other types of idiots, and from pituitary dwarfs is discussed by Means *et al* (1963).

Normal serum PBI levels have been reported in Klinefelter's syndrome (Plunkett, Rangecroft, and Heagy, 1964); various mosaic genotypes (Jagiello, Kaminetsky, Ricks, and Ryan, 1966; Lindsten, Bergstrand, Tillinger, Schwarzacher, Tiepolo, Muldal, and Hokfelt, 1966); Turner's syndrome (Freychet, Rosselin, Assan, Tchobroutsky, Dolais, and Dérot, 1967); cerebral gigantism (Stephenson, Mellinger, and Manson, 1968); the Prader-Willi syndrome (Landwirth, Schwartz, and Grunt, 1968); Seckel's syndrome (Harper, Orti, and Baker, 1967; Hillman *et al*, 1968); and Werner's syndrome (Zucker-Franklin, Rifkin, and Jacobson, 1968).

INFECTIONS

Data on serum PBI levels are lacking for most common infections. One might expect that disturbances of liver function in infection could lead to abnormalities in the serum PBI as a result of changes in the rate of secretion of TBG and possibly of iodoalbumin. In fact high serum PBI levels and

TBG capacity have been reported in the acute phase of infective hepatitis (Vannotti and Béraud, 1959; Lemarchand-Béraud, Assayah, and Vannotti, 1964) and an increased scatter of PBI values with both high and low levels in pulmonary tuberculosis (Klassen, Riley, and Curtis, 1945; Cattaneo, de Simoni, and Fantoli, 1955; de Simoni, 1957) and Chagas, disease (Lomonaco, Oliveira, Kieffer, and Pieroni, 1966). A fall of 0·5-1 μg/100 ml coinciding with a rise in the percentage of free T_4 was observed on the third day of experimental human tularaemia, and a rise of 1-2 μg/100 ml coinciding with a fall in the percentage of free T_4 was observed on the fifth day of the disease (Shambaugh and Beisel, 1967). On the other hand, normal serum PBI levels have been reported in pneumococcal pneumonia (Gregerman and Solomon, 1967) and in leprosy (Sehgal and Basu, 1967).

It seems that changes in the serum PBI in infections are inconsistent and may be absent.

IMMUNOLOGICAL DISORDERS

Abnormal serum PBI levels have not been reported in disorders of immunity unless the thyroid gland is involved in the disease process. The serum PBI is within the normal range in asthma (Dahl, 1964).

NEOPLASTIC DISEASES

Hormone-secreting tumours may cause increases in the serum protein-bound iodine. Three different mechanisms have been demonstrated: (1) oestrogen secretion in hydatidiform mole (Dowling, Ingbar, and Freinkel, 1960b) producing raised TBG; (2) secretion of thyroid-stimulating hormone (TSH) in some cases of chorionepithelioma (Odell, Bates, Rivlin, Lipsett, and Hertz, 1963) and in one case of embryonic carcinoma of the testis (Steigbigel, Oppenheim, Fishman, and Carbone, 1964); and (3) secretion of thyroid hormone by an ovarian dermoid cyst with struma ovarii (Perlmutter and Mufson, 1951). The serum PBI level is normal in phaeochromocytoma although there is hypermetabolism (Beierwaltes, 1956).

There is no evidence of consistent changes in the serum PBI in patients with tumours which do not secrete hormones. Reports that the serum PBI was high in some cases of metastatic carcinoma of the breast (Carter, Feldman, and Schwartz, 1960; Myhill, Reeve, and Hales, 1966) have not been confirmed (Marczynska, Kolodziejska, Glinska, and Adamczyk, 1965). Data which suggested that hypothyroidism was associated with a marginally increased incidence and a poorer prognosis in malignant disease (Liechty, Hodges, and Burket, 1963) have not been generally accepted as evidence of a relation between neoplasia and thyroid state. Sicher and Waterhouse (1967) in a careful study found no evidence to suggest that the progress of carcinoma of the breast was related in any way to the thyroid state of the patient, despite the widespread clinical impression to the contrary.

DISORDERS OF METABOLISM

Hollander *et al* (1967b) reported abnormalities of serum iodine in acute intermittent porphyria. High serum PBI levels were found in four out of 10 male patients and seven out of 17 female patients; high serum TBG capacity in two out of seven male patients and 11 out of 13 female patients; and a PBI-T_4I difference greater than 1 μg/100 ml in three out of 10 female patients and in three out of five male patients. These results suggest that liver function is disturbed. The high PBI-T_4I difference was not commented on by Hollander *et al* (1967b) but might suggest that the liver was producing abnormal amounts of an iodoprotein similar to that described by Surks and Oppenheimer (1969).

Normal serum PBI levels have been reported in phenylketonuria (Leistyna, Hassan, Aplin, and Green, 1964; Rundle, Fannin, and Sylvester, 1966; Tishler and Ingbar, 1966), in episodic ketotic hypoglycaemia of infants (Colle and Ulstrom, 1964), and in progressive partial lipodystrophy, otherwise known as Barraquer-Simon's disease (Rifkind and Boyle, 1967).

The effect of malnutrition on the serum PBI requires further study. Case reports have appeared of low serum PBI levels in severe malnutrition with hypoalbuminaemia (Peters and Man, 1948), in spinal transection with inanition and hypoalbuminaemia (Lloyd, Kaplan, Kupperman, Grynbaum, and Rusk, 1964), and in a number of chronic debilitating disorders which probably involved poor nutrition (Engstrom and Markardt, 1955). The low serum PBI levels are not the direct result of the low serum albumin, since the serum PBI is normal in hereditary analbuminaemia (Hollander, Bernstein, and Oppenheimer, 1968). The low serum PBI levels might result from depression of the thyroid gland, since it has been reported that thyroid ^{131}I uptakes may be low in children suffering from malnutrition (El-Gholmy, Ghaleb, Khalifa, Senna, and El-Akkad, 1967).

The serum PBI is usually normal in obesity (Craig, Ray, Waxler, and Madigan, 1963; Dolecek and Klabusay, 1963; Hortling, de la Chapelle, Frisk, and Widholm, 1964; Benoit and Durrance, 1965). However, a tendency towards low serum PBI levels has been reported in obese patients whose serum free fatty acid level was not reduced by adrenaline (Goldberg and Gordon, 1964). In one group of obese patients fasting lowered the serum PBI level by

1 μg/100 ml and also lowered the thyroid absolute iodine uptake (Alexander, Harrison, Harden, and Koutras, 1964). In another group of obese patients fasting was found not to affect the serum PBI (Schatz, Sheppard, Palter, and Jaffri, 1967). Possibly the level of serum free fatty acids may determine whether a fasting obese patient has a low serum PBI or not, since free fatty acids are known to displace T_4 from TBG (Hollander, Scott, Burgess, Rabinowitz, Merimee, and Oppenheimer, 1967a).

Gout is a complication of myxoedema, particularly in postmenopausal women (Leeper, Benua, Brener, and Rawson, 1960; Ryckewaert, Massé, Jurmand, Caroit, Durieu, Guérin, and de Sèze, 1967), and a low serum PBI may thus be of diagnostic importance.

DISEASES OF ENDOCRINE GLANDS OTHER THAN THE THYROID

The serum PBI may be affected in pituitary disease as a result of disorders in TSH secretion. Hypopituitarism leads to hypothyroidism when the TSH secretion is reduced, but TSH secretion may be spared in some cases so the serum PBI may remain normal (see Wayne *et al*, 1964; Odell, 1966; Spellacy and Cohen, 1967). Normal serum PBI levels have been reported in Cushing's disease (Oppenheimer and Werner, 1966). Acromegaly has an inconsistent effect on the serum PBI, high, low and normal values having been reported in different patients (Hamwi, Skillman, and Tufts, 1960; Kozac, Vagnucci, Lauler, and Thorn, 1966; Inada and Sterling, 1967a; Roth, Glick, Cuatrecasas, and Hollander, 1967). It appears that patients in the active stage of the disease or who have had the disease for more than five years are the more likely to have low serum PBI levels. This partly results from TSH deficiency and partly from a reduction in TBG capacity (Inada and Sterling, 1967a; Roth *et al*, 1967). High serum PBI levels in acromegaly would raise the suspicion of thyrotoxicosis, which is known to occur in association with acromegaly (Roth *et al*, 1967).

Cases of primary Addison's disease have been reported in association with hypothyroidism, Hashimoto's disease, focal lymphocytic thyroiditis, and nodular goitre (Turkington and Lebovitz, 1967), the serum PBI levels being appropriate to the thyroid disorder.

The effect of hormone-secreting ovarian, testicular, and placental tumours on the serum PBI is discussed in the section on neoplastic diseases. The serum PBI is normal in female hirsutism (Wieland, Vorys, Folk, Besch, Neri, and Hamwi, 1966).

Normal serum PBI levels have been reported in testicular deficiency with sexual infantilism (Huffer, Scott, Connor, and Lovice, 1964) and testicular feminization (Walker, Carney, and Gates, 1964). Three cases have been reported in which either ovarian or testicular dysgenesis, multiple congenital abnormalities, and a high level of follicle-stimulating hormone or total gonadotropin excretion were associated with serum PBI levels between 8·3 and 9·4 μg/100 ml (Chokas, 1960; Lundberg, 1966). Possibly these patients could have had high TSH secretion rates as a result of the stimulation of pituitary activity by the low level of circulating gonadal hormones, although they were reported as being clinically euthyroid. A case of juvenile hypothyroidism associated with precocious puberty and an ovarian mass which regressed on T_4 therapy (Wood, Olichney, Locke, Crispell, Thornton, and Kitay, 1965) may represent an instance of the reverse phenomenon in which the pituitary is stimulated to secrete gonadotropic hormone by the low level of circulating thyroid hormone.

Normal serum PBI levels are found in primary gynaecomastia (Rosewater, Gwinup, and Hamwi, 1965), although gynaecomastia which regresses on antithyroid treatment is commonly present in active thyrotoxicosis (Becker, Winnaker, Matthews, and Higgins, 1968).

DISEASES OF THE DIGESTIVE SYSTEM

Hepatocellular disorders may cause abnormalities of the serum PBI, presumably as a result of disturbances in TBG synthesis and possibly also in T_4 metabolism. High serum PBI levels are found in the acute phase of infective hepatitis (Vannotti and Béraud, 1959; Lemarchand-Béraud *et al*, 1964). The serum PBI is usually within normal limits in hepatic cirrhosis (Mueller, Brausch, Hirsch, Benua, and Dobyns, 1954; Shipley and Chudzik, 1957) but occasional results outside the normal range occur, low values being more frequent than high values (Kydd and Man, 1951; Tanaka and Starr, 1959; Bora, Kapoor, Krishnan, and Tandon, 1963; Hollander, Meek, and Manning, 1967c; Inada and Sterling, 1967b).

The serum PBI is normal in obstructive jaundice (Kydd and Man, 1951), acute alcoholism (Selzer and vanHouten, 1964; Augustine, 1967), chronic alcoholism (Selzer and vanHouten, 1964), and pancreatic steatorrhoea (Hiss and Dowling, 1962).

Thyrotoxicosis may present with abdominal pain and vomiting, simulating an acute abdomen (Chapman and Maloof, 1956).

DISEASES OF THE HAEMOPOIETIC SYSTEM

The serum PBI has been reported to be raised in some cases of acute or chronic leukaemia of both lymphocytic and myelocytic types (Shurygin, Komarova, Murchakova, Sokolova, and Tendler, 1967).

This finding requires confirmation since it has been generally accepted that thyroid function is normal in leukaemia despite hypermetabolism (Means *et al*, 1963). Fractionation studies of blood iodine would be of interest to investigate whether abnormal quantities of iodoproteins were present in leukaemia.

The association between pernicious anaemia and hypothyroidism (Irvine, Davies, Delamore, and Wynn-Williams, 1962), thyrotoxicosis (Doniach, Roitt, and Taylor, 1963) or Hashimoto's disease (Irvine *et al*, 1962) is well known.

DISEASES OF THE CARDIOVASCULAR SYSTEM

Unexplained low PBI values have been reported in some inpatients with atherosclerosis (Janotka, Ondrejička, and Pechán, 1967). Normal values have been found in hypertension (Mehbod, Swartz, and Brest, 1967), congestive cardiac failure in euthyroid patients not treated with diuretics (Mehbod, Swartz, and Brest, 1967), idiopathic atrial fibrillation (Peter, Gracey, and Beach, 1968), supraventricular tachycardia (Schatz, 1967), and myocardial infarction (Volpé *et al*, 1960), the last observation not confirming an earlier report of low serum PBI levels in some patients with myocardial infarction (Marmorston, Hoffman, Sobel, and Starr, 1955).

Congestive cardiac failure is a well known complication of thyrotoxicosis (Means *et al*, 1963) and myxoedema heart is also well known (Means *et al*, 1963). An association between hypothyroidism with hypercholesterolaemia and coronary artery disease has been suggested (Azar, 1965).

DISEASES OF THE KIDNEYS

In the nephrotic syndrome the serum PBI is often low when the serum protein disorder is severe, but normal serum PBI levels may occur (Peters and Man, 1948; Perry and Cosgrove, 1949; Kydd, Man, and Peters, 1950; Recant and Riggs, 1952; Rasmusson, 1956; Robbins and Rall, 1957; Robbins, Rall, and Petermann, 1957; Cruchaud, Béraud, Cruchaud, and Vannotti, 1958). The patients tend to be hypometabolic but are not clinically hypothyroid, and appear to have normal rates of T_4 synthesis although the absolute rate of tissue metabolism of T_4 may be low with large urinary losses of T_4 and TBG (Rasmusson, 1956; Cruchaud *et al*, 1958).

In chronic renal failure with uraemia the serum PBI is usually normal, although a few cases with low levels have been reported, possibly as a terminal event (Perry and Hughes, 1952; Engstrom and Markardt, 1955).

DISEASES OF THE LOCOMOTOR SYSTEM AND SKELETON

Epiphyseal dysgenesis and retarded bone growth are recognized complications of juvenile hypothyroidism (Means *et al*, 1963). Signs of thyroid hypofunction or the presence of toxic thyroid adenomas were stated to have been found by isotope studies in seven out of seven patients with Legg-Calvé-Perthes disease (Emerick, Holly, Joistad, and Corrigan, 1954) but normal serum levels were reported in 31 out of another series of 32 cases, the remaining patient having a high serum PBI (Katz, 1955). The existence of an association between Legg-Calvé-Perthes disease and juvenile thyroid disease thus remains an open question.

Osteoporosis with pathological fractures and bone destruction or osteitis fibrosa may occur in the later stages of untreated thyrotoxicosis (Means *et al*, 1963).

Subacromial bursitis occurs in 4% of patients with thyrotoxicosis (Chapman and Maloof, 1956).

DISEASES OF THE SKIN

Although de Mowbray and Tickner (1952) reported low serum PBI levels in nine out of 50 patients with miscellaneous skin disorders, there is no evidence that abnormal serum PBI levels are associated with any particular skin disease. Normal serum PBI levels have been reported in both male and female types of alopecia (Lubowe, 1963).

The skin changes in hypothyroidism and in thyroid acropachy are well documented (Means *et al*, 1963). Peripheral oedema, unaccompanied by renal or circulatory failure, is a rare manifestation of thyrotoxicosis (Chapman and Maloof, 1956; Means *et al*, 1963).

DISEASES OF THE NEUROMUSCULAR SYSTEM

Normal serum PBI levels have been usually found in primary disorders of muscle function, such as progressive muscular dystrophy (Danowski, Sabeh, Vester, Sarver, and Sunder, 1965), and myotonia dystrophica, which is only rarely associated with hypothyroidism, although hypometabolism is present (Stanbury, Goldsmith, and Gillis, 1954; Jacobson, Schultz, and Anderson, 1955; Holland and Hill, 1956). High serum PBI levels were reported in two out of eight patients with ocular myopathy (Lundberg, 1966), but the patients had gonadal dysgenesis and congenital developmental disorders in addition. It is thought more likely that the high serum PBI levels in these patients were related to endocrine imbalance, and they have been discussed in the section on endocrine disease.

Severe myopathy occurs in some thyrotoxic patients (Chapman and Maloof, 1956; Means *et al*, 1963). The sporadic type of periodic paralysis is associated with thyrotoxicosis (Engel, 1961). Myasthenia gravis is also associated with thyrotoxicosis

(Grob, 1958; Szobor and Környey, 1966). In one such myasthenic and thyrotoxic patient, who was on T_4 maintenance therapy after treatment of the thyrotoxicosis by ^{131}I, the myasthenia was exacerbated by any departure from euthyroidism towards either hypothyroidism or hyperthyroidism (Gaelen and Levitan, 1968).

Myxoedema patients may present with a myopathy characterized by muscular stiffness and pain (Means *et al*, 1963).

The serum PBI was found to be normal in patients with Parkinsonism of various aetiologies, although clinically they presented some features of hypothyroidism (Strang, 1968). Normal serum PBI levels have been reported in kuru (Buttfield, Hetzel, and Hornabrook, 1968). Some cases have been reported of diencephalic and hypothalamic tumours associated with signs of hypothyroidism (Buntser, 1965), presumably secondary to disturbances of pituitary function.

Thyrotoxicosis may present as an encephalopathy or an epileptiform seizure (Chapman and Maloof, 1956).

The carpal tunnel syndrome may be a presenting feature of myxoedema (Means *et al*, 1963).

DISEASES OF THE EYE

High serum PBI levels have been observed in superior limbic keratoconjunctivitis (Tenzel, 1968; Theodore, 1968; Cher, 1968), a condition which may be associated with hyperthyroidism or previous hyperthyroidism (Cher, 1968). Superior rectus palsy is an early sign of dysthyroid exophthalmos (Goldstein, 1964).

MENTAL DISORDERS

Evidence of thyroid dysfunction has been sought in mental disorders of various types for many years, but the results have usually been negative. Difficulty arises in this field because groups of patients with the same diagnosis studied by different workers are not necessarily representative of the same clinical entity. Normal serum PBI levels have been reported in toxic psychosis (Bowman, Miller, Dailey, Simon, Frankel, and Lowe, 1950), schizophrenia (Brody and Man, 1950; Bowman *et al*, 1950; Simpson, Cranswick, and Blair, 1964), manic depression (Bowman *et al*, 1950), periodic psychosis (Libow and Durell, 1965), depression (Board, Wadeson, and Persky, 1957; Gibbons, Gibson, Maxwell, and Wilcox, 1960; Nikula-Baumann, Hiisi-Brummer, and Baumann, 1965), mixed psychoneurosis (Bowman *et al*, 1950), and anorexia nervosa (Bowman *et al*, 1950; de Moor and Evenepoel, 1964). The serial PBI measurements in patients with catatonia reported by Gjessing (1964) are difficult to interpret because his patients were treated with seaweed and T_3 and T_4 loads at different stages of his investigation.

Recently, abnormal serum PBI levels have been reported in some patients suffering from affective disorders or from schizophrenia with a high paranoid rating and marked emotional stress (Parhon-Stefanescu, Nikolau, Aurora, Kuku, and Vianu, 1966; Dewhurst, El Kabir, Exley, Harris, and Mandelbroke, 1968; Gosling, 1968). Parhon-Stefanescu *et al* (1966) recorded low serum PBI levels in four out of 16 endogenous depressives, four out of 11 reactive depressives, five out of eight involutional depressives, and 13 out of 27 patients in the depressive phase of manic depression. Dewhurst *et al* (1968) reported that eight out of 20 schizophrenics had at least one high serum PBI reading and five out of the 20 had at least one high blood TSH level, associated with a high paranoid rating. On the other hand, one of their schizophrenics had a persistently low serum PBI level. Dewhurst *et al* (1968) also reported at least one high serum PBI level in 17 out of 44 patients with affective disorders. Of those 17 patients, 11 were in the initial stages of depression. At least one high blood TSH level was found in 16 of the 44 patients, of whom 15 patients were suffering from depression and one from hypomania. Dewhurst *et al* (1968) reported that high TSH levels and high PBI levels were not always found in the same blood sample and suggested that changes in TBG capacity might have occurred in some of their patients. Nevertheless they concluded that emotional stress in psychiatric patients might increase TSH secretion. Gosling (1968) stated that elderly patients with agitated depression tended to have high serum PBI levels, which fell on remission of the psychiatric disorder. On the other hand, Libow and Durell (1965) described a schizophrenic patient with a periodic psychosis, whose serum PBI and thyroid ^{131}I uptake tended to rise on transition from hyperactivity to muteness, and *vice versa*, presumably as a result of changes in TSH secretion rate.

Parhon-Stefanescu *et al* (1966) did not report any studies of thyroid function in their patients other than the serum PBI, and it is possible that hypothyroidism was an aetiological or precipitating factor in the psychiatric disorders of their patients with low serum PBI levels. This may also have been the case in the schizophrenic with a low serum PBI reported by Dewhurst *et al* (1968). The finding by Dewhurst *et al* (1968) of high serum PBI levels in emotionally stressed psychiatric patients is consistent with the study of Levi (1967) in which severe emotional stress caused significant elevation of serum PBI in normal subjects. Gosling (1968) suggested that the thyroid reserve might fall as a result of

continued stimulation over a long period in agitated depressives.

The onset of an attack of thyrotoxicosis is often associated with a history of recent psychological trauma (see Means *et al*, 1963) and severe mental disorders may occur in myxoedema in adults, both untreated and on commencing T_4 therapy (see Means *et al*, 1963).

Drugs which May Affect the Serum PBI

Drugs which alter the serum PBI level may be grouped into seven classes: (1) goitrogens, (2) drugs which affect T_4 transport, (3) drugs which affect the uptake and metabolism of T_4 by tissues, (4) drugs used in thyroid replacement therapy, (5) other drugs which contain iodine, (6) drugs which interfere with the chemistry of PBI determinations, and (7) drugs which have been reported to affect the serum PBI without elucidation of the mechanism responsible. It is also helpful for diagnostic purposes to know if a drug has been shown not to affect the serum PBI level.

The widespread use of the red dye, erythrosine (tetra-iodofluorescein), to colour proprietary pharmaceuticals is a serious source of contamination (Andersen, Keiding, and Nielsen, 1964; Bora, Radichevich, and Werner, 1969). Enquiry should be made whether the patient is taking any red-coloured preparations before taking blood for a serum PBI estimation.

The effect of drugs on the serum PBI is discussed in general terms in this section. Supplementary information on specific products is included in the Appendices.

GOITROGENS

Goitrogenic substances interfere with the synthesis of thyroid hormone, thereby causing hypothyroidism with a low serum PBI level. The development of goitre results from an increase in the secretion of thyroid-secreting hormone. Goitrogenic drugs are of two main types (Wayne *et al*, 1964). The first type, of which perchlorate is an example, interferes with the trapping of iodide by the thyroid gland. The second type, of which thiouracil is an example, inhibits the iodination of tyrosine residues in thyroglobulin. Several of the more powerful goitrogens are used for the medical treatment of thyrotoxicosis.

DRUGS AFFECTING T_4 TRANSPORT IN SERUM

Drugs may affect the T_4-binding capacity of serum in three ways. They may cause an increase, eg, oestrogens (Dowling, Freinkel, and Ingbar, 1956b) or a decrease, eg, androgens (Federman, Robbins, and Rall, 1958) in the number of serum T_4-binding sites, or they may compete with T_4 for the existing T_4-binding sites, eg, salicylates (Austen, Rubini, Meroney, and Wolff, 1958). Drugs which reduce serum T_4-binding capacity or which compete with T_4 for binding sites may cause low serum PBI levels to be found in euthyroid individuals, whereas drugs which increase T_4-binding capacity may give rise to high serum PBI levels in euthyroid individuals.

DRUGS ALTERING THE UPTAKE AND METABOLISM OF T_4 BY TISSUES

It has been found that diphenylhydantoin, which competes with T_4 for TBG (Oppenheimer and Tavernetti, 1962), also causes a reduction in the absolute free T_4 concentration. Chin and Schussler (1968) suggested that diphenylhydantoin increased the rate of uptake and degradation of T_4 by the liver (see also Oppenheimer, Bernstein, and Hasen, 1967). Hersham (1964) reported that 5-propylthouracil and 6-propylthouracil increased the serum PBI of patients being treated with T_4 and perchlorate by 0·8 μg/100 ml, presumably by reducing peripheral metabolism of T_4.

DRUGS USED IN THYROID REPLACEMENT THERAPY

Serum PBI levels in patients on thyroid maintenance therapy are usually within normal limits if desiccated thyroid is used, high if T_4 alone is used, and low if T_3 alone is used (Lavietes and Epstein, 1964; Alley, Danowski, Robbins, Weir, Sabeh, and Moses, 1968). T_4 is more strongly bound to TBG than T_3, hence T_3 is more active in physiological conditions than T_4 (Oppenheimer *et al*, 1963). The serum concentration of T_3 required to maintain a subject in the euthyroid state is thus less than the corresponding serum concentration of T_4. Desiccated thyroid provides a thyroid hormone preparation in which the ratio of T_3 to T_4 approximates to that of the normal thyroid secretion and normal PBI levels are usually found when these preparations are used. In the case of one thyroid preparation (Proloid), administration of adequate maintenance doses was associated at one time with low PBI levels, perhaps because the method of preparation then in use resulted in a high T_3 content (Braverman and Ingbar, 1964).

The possibility exists that a thyroid preparation given orally could cause a temporary elevation of serum PBI which would be sufficiently large to give misleading results. Myant and Pochin (1950) found that after an oral dose of 80 μg of [^{131}I] T_4, a maximum of 4 to 5% of the dose was present per litre of plasma, the peak activity occurring two to three hours after administration and falling off very

slowly over 24 hours. An oral dose of 0·3 mg of T_4 would thus be expected to raise the serum PBI by 1·5-2 μg/100 ml after two to three hours. This effect is not large enough to be responsible for the high PBI levels in T_4-treated patients, but should be borne in mind in interpreting serial variations in the serum PBI of these patients.

IODINE-CONTAINING PREPARATIONS OTHER THAN THYROID MEDICATIONS

Iodine drugs may cause high serum PBI levels if they contain sufficient iodine in a form which is precipitable with serum proteins. These products mostly fall into one of the following groups: (1) radiographic contrast media, (2) amoebicides and intestinal disinfectants, (3) expectorants, (4) topical applications (lotions, ointments, skin disinfectants, and cosmetics), and (5) vitamin-mineral preparations.

Organic iodine compounds which are precipitated with the serum PBI are often protein-bound and long-acting (Heijdemann and Lindeboom, 1958). Some are metabolized and may cause elevations of plasma inorganic iodide (Chaney, 1958), which lead to a reduced thyroid ^{131}I uptake (Sendrail, Bru, and Bloom, 1966).

Preparations containing relatively small doses of inorganic iodide reduce the thyroid ^{131}I uptake without affecting the serum PBI (Slater and Numeroff, 1961). Doses of 1 g of iodide per day increase the serum PBI (Fisher *et al*, 1965). Heavier dosage over a long period leads to iodide goitre (see above) associated with the presence of an abnormal serum iodoprotein (Danowski *et al*, 1950).

The effect of inorganic iodide on the serum PBI usually lasts a few weeks. Organic iodine compounds may persist longer in the serum. Radiographic contrast media are particularly troublesome. Elevations following intravenous pyelography tend to persist for several days or a few weeks, those following cholecystography persist for months up to many years with transplacental contamination in the case of Teridax, and those following bronchography or myelography persist for many years (see reviews by Sisson, 1965; and Davis, 1966). Placental arteriography within 14 days of birth has been reported to cause a raised serum PBI in the neonate for six to eight months (Similä, Rosberg, and Pystynen, 1967).

INTERFERENCE WITH THE ANALYTICAL METHOD

Heavy metals are the most important source of interference with the chemistry of PBI determinations. Mercury and its salts interfere with the digestion and distillation steps in wet ashing methods and with the catalytic determination of iodide by the ceric-arsenite reaction (Myers and Man, 1951; Zak, Willard, Myers, and Boyle, 1952). The administration of mercurial diuretics to the patient may cause low results to be obtained in PBI analyses performed by the acid distillation or chloric acid digestion techniques (Myers and Man, 1951; Zak *et al*, 1952). A 24-hour period following the administration of the drug is usually sufficient to allow the drug level to decrease below the interference level, although 48 hours may be necessary to allow excretion of the drug if the diuretic is unsuccessful (Myers and Man, 1951; Barker, 1955). Schteingart, Perlmutter, and Numeroff (1960) found a mean decrease of 0·24 μg/100 ml in the serum PBI four hours after a dose of meralluride when using an alkaline ashing method, but there was no residual effect after longer periods. The difference at four hours was not statistically significant, but the results of Schteingart *et al* (1960) do not exclude interference by mercurials with PBI determinations by alkaline ashing. It is theoretically possible that mercuric iodide could be volatilized at the temperatures used for alkaline ashing (600°C). The degree of protein binding of the mercurial might also be a factor in determining whether it would interfere with the analysis.

Therapy with gold salts causes very low serum PBI levels determined by the chloric acid digestion method because gold salts interfere with the ceric-arsenite reaction which is used to estimate iodine in the digest (Fisher, Levy, and Price, 1965). Presumably similar interference would occur if an alkaline ashing method was used.

Copper in distilled water may interfere with PBI determination by acid digestion according to Means *et al* (1963), but it is not clear from their statement whether the digestion or the estimation step is affected.

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Appendix I

List of Drugs which May Cause Disturbances in the Serum Protein-bound Iodine

Drugs marked with an asterisk are considered likely to interfere with serum PBI determinations in therapeutic doses.

DRUGS AND PREPARATIONS CONTAINING IODINE

The drugs and preparations listed in this section, with the exception of a few for which specific references are given, appear in Martindale's *Extra Pharmacopoeia* (25th ed, 1967), in Medindex (Jan.-March 1967) or in Wayne *et al* (1964, Appendix II). Some pharmacological details were obtained from *Iodine Pharmaceuticals* (1952, 3rd supplement, 1956) published by the Chilean Iodine Educational Bureau, which contains an extensive list of iodine preparations, including many less common ones. Further data were kindly provided by Dr W. W. Snedden of the Chilean Iodine Educational Bureau and by the Library of the Pharmaceutical Society.

All the compounds listed in this section contain iodine in inorganic or organic combination, and either have been reported to, or could potentially, affect tests of thyroid function. This does not, however, mean that changes in serum PBI would necessarily follow their administration. Their possible effect on the serum PBI of an individual patient must be assessed in relation to the dose taken and to the composition of the preparation concerned.

Topical applications (including antiseptics and oral disinfectants)[1]
Acnosil contains iodine (quantity unspecified)
Adrepatine suppositories contain 10 mg fresh thyroid gland

[1]Some sun tan oil preparations contain iodine (Chapman and Maloof, 1955).

Anerythene (= H.E.B. 'A')
Antiru cream contains 0·0125% NaI
Arctic Glow menthol and wintergreen cream contains 1% KI
*Arthene volatile iodine rub contains 0·25% phenylethyl iodide (57% I) and 1% terpineol iodide (45·5% I)
*Ayrton's iodized throat tablets contain 0·3 mg of I_2 and 0·3 mg of KI

*B.F.I. powder contains 16% w/w bismuth-formic-iodide
Balmosa iodized contains 1·2% NaI
Balto foot balm contains 0·25% KI
*Barquinol cream contains clioquinol (concentration not specified)
*Betadine (= Povidone Iodine)
*Betnovate-C contains 3% clioquinol
*Bijogalum (= bismuth oxyiodogallate)
Bismoid contains sodium resorcinol iodide (quantity not specified)
*Bismuth-Formic-Iodide. A mixture containing thymol iodide and bismuth oxyiodide
*Bismuth oxyiodide contains 35% I
*Bismuth oxyiodogallate contains at least 20% I
*Bismuth oxyiodosubgallate (= bismuth oxyiodogallate)
*Calmitol ointment contains 9·6 mg of I_2 per 100 g
*Calot's fluid contains 10% iodoform
*Calot's no. 2 paste contains 4% iodoform
Chibret iodo-chloride collyrium contains 0·5% KI
*Cor-Tar-Quin contains 1% di-iodohydroxyquinoline
Cuprodine contains 0·1% lauryl iodide (31% I)

*Diphenyliodinium phthalimide contains 39% I
*Diphenyliodonium acetate contains 43% I
*Diphiodin 1.G.62 (cream or solution) contains 0·3% I (organic)
Dols' impregnated flannel (impregnating solution contains 1·25% I_2)
Dols' rub cream contains 0·25% KI
*Domeform—HC contains 3% clioquinol
*Donovan's solution contains 1% AsI_3 and 1% HgI_2

*E.D.P. (Evans dusting powder) contains 4·18% bismuth oxyiodide and 1·14% thymol iodide
*Ecothiopate (iodide) contains 33% I
*Echothiopate (= Ecothiopate)
Endoarsan contains 0·2% NaI and 0·1% HgI_2

*Faringets lozenges contain 0·8 mg of I (organic)

*H.E.B. 'A' contains 0·19% I (organic)
*H.E.B. S.S. contains 0·5% diphenyliodonium acetate
*H.E.B. calamine cream contains 0·5% diphenyliodonium acetate
*Hamolen suppositories contain bismuth oxyiodogallate and tri-iodoresorcinol

*I.B. paint contains 1·25% I_2 and 1·25% KI
*Iglodine contains 0·04% combined iodine
*Iglodine ointment contains 0·14% combined iodine
*Iglodine salicylated contains 0·32% combined iodine
*Iodex contains 4% I_2
*Iodine glycerin contains 2·28% I_2 and 6·86% KI
Iodized cream (Thomson's) contains 0·05% NaI
*Iodoform contains 97% I
*Iodoglycerin solution (= iodine glycerin)
*Iodopix contains 1% clioquinol

*Locorten-Vioform contains 3% clioquinol
Lumuscoba impregnated pad. Impegnating solution contains 0·4% NaI

Medicoids suppositories contain 0·5% bismuth oxyiodide
*Mencières solution A contains 10% iodoform
*Mencières solution B contains 1% iodoform
*Mentex embrocation contains 0·075% I_2
*Morton's fluid (= iodine glycerin)

N.H. & S. balm contains 0·009% combined iodine
*N.P.U. liquid antiseptic contains 0·15% I_2
*Nasciodine contains 1·25% I_2
Neoprotosil ointment contains 1% AgI
*Nystaform—HC (lotion or ointment) contains 3% clioquinol

*Parisepsin diphiodin contains diphenyliodinium phthalimide (concentration not stated)
*Paton's mouth treatment contains 0·05% iodoform

*Phospholine (= Ecothiopate)
*Povidone-Iodine contains 9-12% available iodine
*Proviodine (= Povidone-Iodine)

*Quinaband zinc paste and calamine bandage contains clioquinol

*Radosene contains 2% phenylethyliodide (55% I)
Riddorheum liquid contains 1·2% NH_4I
*Rozental's paste contains 2% w/w I_2

*Scholl's (Dr) bunion lotion contains 2·7% I_2 and 2·7% KI
*Sedresol ointment contains 0·42% thymol iodide
Sorosil contains 0·006% I_2
Sure Shield iodized throat lozenges contain 0·0478% I_2 (free and combined)
Surgaseptic antiseptic throat tablets contain 0·075% w/w of organically bound iodine
Surgaseptic effervescing mouth wash tablets contain 0·15% w/w of organically bound iodine
*Surgaseptic germicide contains 0·15% of organically bound iodine
*Surgaseptic ointment contains 12·75 mg of organically bound iodine per 100 g
*Surgaseptic pile suppositories contain 1·5 mg of organically bound iodine
*Synalar-C ointment contains 3% clioquinol

*T.B.P. hair and scalp treatment contains 0·01% 'iodosalicylic' acid
*T.C.P. B_2 colloidal emulsion contains 0·08% of organically bound iodine
*T.C.P. first aid cream contains 0·04% of organically bound iodine
*T.C.P. liquid antiseptic contains 0·11% of organically bound iodine
*T.C.P. ointment contains 0·07% of organically bound iodine, 0·01% I_2 and 0·02% KI
T.C.P. throat pastilles contain 0·01% of organically bound iodine
*Talbot's solution contains 4·1% I_2 and 2·5% ZnI_2
*Thymol iodide contains 43% I
*Tucal lozenges contain 0·03% iodophenol (57·5% I)

*Ucal safety first iodized throat lozenges contain 0·2 mg of I_2 and 0·4 mg of KI
*Undecoylium chloride-iodine contains about 40% I

*Vanodine contains 1·9% of available iodine
*Venotone cream contains 0·009% w/w I
Verucol contains 0·1% HgI_2
Virac (= undecoylium chloride-iodine)

Wismutoxyjodidgallat (= bismuth oxyiodogallate)

Expectorants, antispasmodics, diuretics, and analgesics
AM 49 contains KI (quantity not specified)
Aciform II (for arthritis) contains iodine (quantity not specified)
Alogeral contains iodocasein (quantity not specified)
*Alostorin tablets contain 0·075 g of iodocasein
*Ambrosia lactation tablets contain 30 mg of I_2
Aminocortiode (composition not stated)
Aminural contains KI (quantity not specified)
*Amiodoxyl benzoate (= ammonium *o*-iodoxybenzoate)
*Ammonium *o*-iodoxybenzoate contains 45% I
*Amsa tablets contain 65 mg of KI
Analeptine contains NaI (concentration not specified)
Antipyrine iodide (= phenazone iodide)—not manufactured now
*Anaspasmine contains 1·3% KI
*Antasma tablets contain 12·28% KI
*Anti-arthritis tablets (Sumner) contain 195 mg of KI
*Asthma Dellipsoids D17 contain 22 mg of CaI_2
Auricol contains SrI_2 (concentration not specified)
Aurubin contains AuI_3 and CaI_2 (concentrations not specified)

Bellapurin suppositories contain 0·002 g of SrI_2
Bethiodyl contains KI (concentration not specified)
Broncholysin contains organic iodine (compound and quantity not specified)
*Bronchotone contains 1·15% NaI
*Brovonex contains 5% caffein and sodiod and 3·25% NaI

*C.M.P. asthma remedy contains 8·3% caffein and sod iod, 8·3% NaI and 0·625% HI

Caffedrin contains di-iodocaffein hydroiodide (quantity not specified)
*Caffein and sod iod (B.P.C.) contains 50-53% NaI
*Caffeine iodide (= di-iodocaffeine hydriodide)
*Caffeine tri-iodide (= di-iodocaffeine hydriodide)
*Caffexen contains 9·14% caffein and sod iod and 9·14% NaI
*Calcidin contains 15% of available iodine
*Calcidrine syrup contains 4% KI
*Candine contains 5·4% di-iodocaffeine hydriodide
*Caphedrodine contains 9·1% caffein and sod iod and 9·1% NaI
Colloidine contains 'colloidal iodine' (quantity not specified)
Colsalide contains KI (quantity not specified)
*Creolix contains 2·5% NaI

*Dainite KI (Grayson, 1960)
Deka contains KI (quantity not specified)
*Di-iodocaffeine hydriodide contains 66·5% I

*Epicaffneine contains 9·1% caffein and sod iod, 9·1% NaI and 0·83% HI
*Ephedrine compound elixir contains 1·25% NaI
*Euphorbia (as mist euphorbia Co) contains 3·4% KI
*Eupinal contains 6·9% NH_4I
*Eupnine contains 14% di-iodocaffeine hydriodide

*Felsol powders contain 12 mg of I_2 combined with 18 mg of phenzone

*Hair's (Dr) asthma remedy contains 0·3% NaI and 5·1% KI
*Hair's (Dr) asthma remedy pastilles contain 14·6% w/w KI and 0·7% w/w NaI
*Halotheine contains 5·4% of iodine combined with caffeine
*Hyodin contains 1·4% I (as HI)

*Iod Calcium Diuretin tablets contain 100 mg of KI
*Iodinated glycerol contains 50% I (organic)
*Iodo-caffedrin contains 10% caffeine and potassium iodide and 3·65% KI
*Iodocaffeine (= caffein and sod iod)
*Iodoephedrine contains 2·55% NaI
*Iodopropylidene dioxypropanol (= iodinated glycerol)
*Iodopropylidene glycerol (= iodinated glycerol)
*Iodopyrine (= antipyrine iodide). See Hydovitz and Rose (1956)

*Kaladex contains 4·4% KI

*Lobidine contains 0·45% KI
*Luma antirheumatic compound contains 0·5% KI
*Luma antirheumatic cubes contain 0·4% w/w KI
*Lydrin contains 4·2% NaI

*Naiodine contains 2% NaI
*Naiodine B contains 5% NaI
*Norisodrine syrup contains 3% CaI_2

*Organidin elixir contains 1·2% iodinated glycerol
*Organidin solution contains 5% iodinated glycerol
*Organidin tablets contain 30 mg of iodinated glycerol

Pulmocardine contains KI and di-iodocaffeine hydriodide (quantities unspecified)

*Rybarex inhalant contains 0·1% tri-iodophenol (81% I)
*Rybronsol powders each contain 30 mg of 'iodophenazone'

*Sibec elixir contains 3·5% NaI

*Theomine tablets contain 162 mg of KI
*Theo-Organidin contains 0·2% iodinated glycerol
Thioderazine contains organic iodine (nature and concentration not specified)
*Trisan contains 6·05% KI
*Tucal linctus contains 0·02% iodophenol (57·5% I)

Intestinal disinfectants (including anthelminthics and amoebicides)
*Abitrene (= di-iodohydroxyquinoline)
*Amebastar (= di-iodohydroxyquinoline)
*Amoebindon (= di-iodoquinoline)
*Amoequin (= di-iodoquinoline)
*Anelmid (= diathiazanine iodide)
*Avlochin (= chiniofon)

*BW 61-32 (= stilbazium iodide)

*Carbantran contains 10% of a Bi derivative of clioquinol
*Chiniofon contains 27·5% I
*Chinioform (= clioquinol)
*Chloroiodohydroxyquinoline (= clioquinol)
*Clioquinol contains 41% I (see Sendrail *et al*, 1966; Sönksen, Ekins, Stevens, Williams, and Nabarro, 1968)
*Cloquinate contains 25% I

*Delvex (= diathiazanine iodide)
*Diathiazanine iodide contains 24·5% I
*Di-iodohydroxyquinoline contains 65% I
*Di-iodoquinoline contains 67% I
*Diodoquin (= di-iodohydroxyquinoline)
*Diodoxyquinoline (= di-iodohydroxyquinoline)
*Direxiode (= di-iodohydroxyquinoline)

*E.B.I. (= emetine and bismuth iodide) contains 40% I
*Embequin (= di-iodohydroxyquinoline)
*Enteroquinodine (= di-iodohydroxyquinoline)
*Enteroquinol (= clioquinol)
*Enterosan tablets contain 100 mg of di-iodohydroxyquinoline
*Enteroseptol (= clioquinol)
*Enterovioform tablets contain 250 mg of clioquinol
*Entrin (= clioquinol)
Esjodin II contains iodine (quantity not specified)

*Floraquin tablets contain 100 mg of di-iodohydroxyquinoline

*Iodochlorhydroxyquin (= clioquinol)
*Iodochlorhydroxyquinoline (= clioquinol)
*Iodoquinoline (= chiniofon)
*Iodoquinoline sulphonic acid (= chiniofon)
*Iodoquinoline sulphonic acid with sodium bicarbonate (= chiniofon)
*Iodothymol contains 46% I
*Iquinol (= di-iodohydroxyquinoline)

*Moebiquin (= di-iodohydroxyquinoline)
*Monopar (= stilbazium iodide)

*Nivembin tablets contain 300 mg of di-iodohydroxyquinoline

*Pabirex contains 1·75% clioquinol
*Partel (= diathiazanine iodide)

*Resotren tablets contain 500 mg of cloquinate
*Resotren compositum tablets contain 75 mg of cloquinate and 300 mg of di-iodohydroxyquinoline

*Savorquin tablets contain 200 mg of di-iodohydroxyquinoline
*Stilbazium iodide contains 22% I

*Telmid (= diathiazanine iodide)
*Tourista tablets contain 250 mg of clioquinol
*Tramil tablets contain 250 mg of clioquinol
*Travelettes for diarrhoea contain 250 mg of clioquinol
*Treps contain 250 mg of clioquinol
*Tridia sachets contain 125 mg of clioquinol
*Turistum contain 90 mg of clioquinol
*Vioform contains 3% clioquinol

Thyroid medications and iodine preparations for internal administration
*Alphidine tablets contain 30 mg of 'assimilable organic iodine'

*Bladderwrack contains up to 0·2% I

*Butyl di-iodohydroxybenzoate contains 57% I
Cavolysin masc and fem (ampoules or tablets) contain 60 mg thyroid
*Choloxon (= dextrothyroxine)
Conthyrin contains thyroxine and methylthiouracil

*Dethyrona (= dextrothyroxine)
*Dextrothyroxine contains 65% I
*Diobene (= butyl di-iodohydroxybenzoate)
*Diotroxin tablets contain 90 μg thyroxine and 10 μg liothyronine
Diuposan tablets contain 130 mg thyroid

Elityran tablets contain 90 mg thyroid
Eltroxin (= thyroxine)
Esjodin I contains iodine (quantity unspecified)

*Fucus (= bladderwrack)

Glandiposan tablets contain 150 mg thyroid

Hormotone tablets contain 6·5 mg thyroid
Hormotone T tablets contain 3·25 mg thyroid

Incretone contains acid extract from 130 mg of thyroid in each 100 m
Iodal tablets contain I_2 and KI (quantities not specified)
*Iodalose contain 3% I (in organic combination with peptone)
Iodamelis P contains an iodine-tannin complex (nature and quantity not specified)
*Iodhema contains 11·25% I (organically bound)
*Iodobehenate (calcium) contains 23·5% I
*Iodobesin tablets contain 5 mg lipid-free thyroid and 50 mg iodalbumin (21·5% I)
*Iodocasein contains 15-20% I
*Iodotannic syrup contains 1% w/w I_2
*Iosal tablets contain 30 mg thyroid and 30 mg 'assimilable organic iodine'

*Kelpware (= bladderwrack)

*Levaxin (= thyroxine)
*Liothyronine contains 58·5% I
*Lugol's solution contains 5% I_2 and 10% KI
*Lusty's Kelgar perles contain 200 mg bladderwrack
*Lusty's Malted Kelp tablets contain 800 mg bladderwrack

Oestrol tablets contain 22 mg thyroid
Orchitone tablets contain 22 mg thyroid

Proloid (= thyroid)

*Saiodine (= calcium iodobehenate)
Scripac (= thyroid)
*Seawrack (= bladderwrack)
*Synthroid (= thyroxine)

*Tertroxin (= liothyronine)
Thionaiodine V tablets contain NaI (quantity not specified)
Thyranon (= thyroid)
Thyreototal (= thyroid)
Thyroboline (= thyroid)
Thyrodex tablets contain 30 mg thyroid
Thyroglobuline thyroid protein containing not less than 0·3% I
Thyroid (B.P.) contains 0·25% I
Thyrophem tablets contain 30 mg thyroid
Thyropit tablets contain 200 mg thyroid
*Thyroxine contains 65% I
*Tri-iodothyronine (= liothyronine)

Vitamin-mineral and dietary preparations[2]

Avozan 4 capsulettes (daily dose) contain 0·1 mg I
Azymil capsules contain 0·1 mg I

Complan contains 44 μg I/100 g

Dekrasil capsules contain 150 μg I

Gevrabon (Grayson, 1960)
Gevral capsules contain 10 μg I (as KI)

*Iodized codliver oil contains 0·1% w/w I
Iodized vitamin capsules (Thomson) contain 150 μg I

McClung Vi-Tabs contain 0·15 mg I (as KI)
*Metrecal (Steinberg and Leifheit, 1965)
Micebrin (Grayson, 1960)

Selora (salt substitute) contains 0·01% w/w KI
Supavite capsules contain 150 μg I
Super Plenamins capsules contain 150 μg I

[2]Complevite and Pregnavite contain traces of iodine and Sanatogen selected multivitamins contain iodine (exact quantities not specified).

Totavite capsules contain 0·1 mg I (as KI)

Unicap capsules (Grayson, 1960)

Vibolex tablets contain 0·05 mg KI
Vykmin black capsules contain 0·2 mg KI
Virol contains 265 μg I/100 g

RADIOGRAPHIC CONTRAST MEDIA

Apart from barium sulphate, all radiographic contrast media contain iodine. The effect of the majority of such compounds on the serum PBI has not been reported. However, all those which have been studied caused elevations of serum PBI, ranging from a few days to at least 30 years.

Individual contrast media are not listed here. Lists are given in Martindale's *Extra Pharmacopoeia* (25th ed, 1967), and in *Iodine Pharmaceuticals* (1952 and 3rd supplement 1956, published by the Chilean Iodine Educational Bureau). It may be assumed that all radiographic contrast media (other than barium sulphate) will cause false raised levels of the serum PBI which may often persist for several months or years. The effects of intravenous aqueous contrast media are usually shortlived (several days to a few weeks), gallbladder contrast media are often of intermediate life (one to three months) whereas those of oily media for bronchography or myelography and some gallbladder contrast media may persist for years (see Sisson 1965; Davis 1966).

Miscellaneous

Activin contains iodinated casein (concentration not stated)
Algocor (= 2 ethyl-(3:5 diiodo-4 hydroxybenzoyl) 3-benzofuran)
Antilusin (= pentamethonium iodide)
Arocalcin (Pitman-Moore Division of Dow Chemical Corp., Indianapolis, USA)
Arteriodon contains hexamethyldiaminoisopropanol di-iodide (quantity not stated)
Aurum Ambrosium contains 0·001% KI

*Benziodarone (Harrison and Cameron, 1965) contains 46% I
*Bi-Iochinol contains 8% quinine iodobismuthate
*Bismosalvan contains 10% quinine iodobismuthate
*Bromsulphthalein. Some batches contaminated with organic iodine (Pileggi, Segal, and Lanchantin, 1963)

*Cardivix (= benziodarone)
Chlorosane tablets contain iodine (quantity not stated)
*C-Van contains 1·5% available iodine

*Darbid (= isopropamide iodide)
*Decamethonium iodide contains 49·5% I
*Dimethyltubocurarine iodide contains 35% I

Ekner Seltzer contains 0·01% NaI
Endoiodine contains hexamethyldiaminoisopropanol di-iodide (quantity not stated)
Endojodin contains hexamethyldiaminoisopropanol di-iodide (quantity not stated)
*Entodon (= hexamethyldiaminoisopropanol di-iodide)
*Erythrosine (tetraiodofluorescein) red colorant for food and drugs (Andersen *et al*, 1964).
Eskornade spansule contains 5 mg isopropamide iodide
Eskornade syrup contains 15 mg isopropamide iodide per 100 ml
*Estomycin (= penethamate hydriodide)
*Estopen (= penethamate hydriodide)

*2-Ethyl (3:5 diiodo-4-hydroxybenzoyl) 3-benzofuran (Andreoli and de Luca, 1964)

*Eulissin (= decamethonium iodide)
*Flaxedil (= gallamine triethiodide)

G.S. tablets contain 8 mg KI
*Gallamine triethiodide contains 42·5% I
Gibert's syrup contains 50 mg HgI_2 per 100 g and 2·5% w/w KI

Hall's wine contains not less than 103 μg I per 100 ml
Halmagon tablets contain 30 μg of MgI_2
*Hexamethyldiaminoisopropanol di-iodide contains 59·5% I

*5-Iodothiouracil (Starr, Petit, Chaney, Rollman, Aiken, Jamieson, and King, 1950; Bondy, 1951)
Isopropamide iodide contains 64% I
*Itrumil (= 5-iodothiouracil)

*Leocillin (= penethamate hydriodide)
Limodin (Central Pharmaceutical Co., Indianapolis, USA) contains KI (quantity not stated)
*Liquor Iodo-Creosotal contains 0·18% I in combination with peptone
*Lysanthine Astier (= Lyxanthine) contains 12% sodium iodopropanol sulphonate (39% I)

*Metubine iodide (= dimethyltubocurarine iodide)

*Natex 'Four', 'Five', and 'Nine' contain 10% seaweeds
*Natex 'Thirty-One' contains 15% seaweeds
*Natex 'Twenty-Two' and 'Thirty-Two' contain 20% seaweeds
*Natex 'Eleven' contains 50% seaweeds
*Neobismosalvan contains 10% quinine iodobismuthate
*Neopenil (= penethamate hydriodide)
*Niblett's (Dr) nerve sedative contains 3·63% KI

*Penethamate hydriodide contains 22·5% I
*Pentamethonium iodide contains 57·5% I
*Perphenazine (some formulations may contain iodinated contaminants—Hansen and Siersbaek-Nielsen, 1967)
Potter's herbal blood compound contains 0·24% KI
Priamide (= isopropamide iodide)
*Pralidoxime (iodide form). See Kondritzer, Svirblis, Goodman, and Paplanus (1968)
Procol capsules contain 2·5 mg isopropamide iodide

*Quinine iodobismuthate contains 57% iodine

*Seaweed (see bladderwrack)
Stelabid tablets contain 5 mg isopropamide iodide
*Syncurine (= decamethonium iodide)

*Tetraiodofluorescein (= erythrosine)
Tyrimide (= isopropamide iodide)

GOITROGENS

Goitrogens are defined as substances which interfere with the synthesis of thyroid hormone by the thyroid gland and are capable of producing thyroid enlargement (see Wayne *et al*, 1964). They may act on the iodide trapping mechanism (perchlorate type), on organic iodine synthesis (thiouracil type), or peripherally on T_4 reabsorption (soya bean). The mechanisms of goitrogenic action of fluorides (Galletti and Joyet, 1958) and lithium carbonate (Sedvall, Jönsson, Petterson, and Levin, 1968) have not been elucidated. The effect of chlorpropamide treatment on the thyroid in diabetic patients is controversial. Hunton, Wells, and Skipper (1965) reported that clinically hypothyroid diabetic patients showed rises in serum PBI levels from hypothyroid levels on withdrawing chlorpropamide. On the other hand, Burke, Silverstein, and Sorkin (1967) did not observe any difference in serum PBI levels between groups of diabetics on chlorpropamide and on insulin. Burdick and Brice (1968) reported that serum PBI levels in sulphonylurea-treated diabetics were lower than in patients treated by insulin and diet, but that they were not usually in the hypothyroid range. These findings reflect the notorious difficulty in diagnosing borderline hypothyroidism and suggest that other factors, eg, varying individual susceptibility to chlorpropamide, dietary goitrogens, or iodide intake, may influence the response of the thyroid to chlorpropamide.

Goitrogens include antithyroid drugs which are used to treat thyrotoxicosis. Small doses of these drugs have no effect on the serum PBI since the rate of thyroid hormone secretion is maintained by a compensatory increase in TSH secretion. Doses large enough to cause hypothyroidism will lead to a reduction in the serum PBI level. Propylthiouracil reduces peripheral deiodination of T_4, particularly in thyrotoxicosis (Hershman, 1964; Furth, Rives, and Becker, 1966), but this is not important diagnostically.

Goitrogen	*Reference*
Perchlorate Type	
Bi-iodate	Wyngaarden, Wright, and Ways (1952)
Chlorate	Wyngaarden *et al* (1952)
*Difluorophosphate	Anbar, Guttmann, and Lewitus (1959)
Fluoride (probably)	See above
*Fluoroborate	Anbar *et el* (1959)
Hypochlorite	Wyngaarden *et al* (1952)
Iodate	Wyngaarden *et al* (1952)
*Monofluorosulphonate	Anbar *et al* (1959)
Nitrate	Wyngaarden *et al* (1952)
*Perchlorate	Wyngaarden *et al* (1952)
*Periodate	Wyngaarden *et al* (1952)
Thiouracil Type	
*Acetazolamide	Gabrilove, Alvarez, and Soffer (1958)
ACTH	Notter (1962)
*α-amino-β-hydroxy butyrate	Greggia, Maggi, Mucci, Patrignani, and Sternieri (1968)
*Amino-glutethimide	Rallison, Kumagai, and Tyler (1967)
*Aminotriazole	Alexander (1959)
*Amphenone	Selenkow, Rivera, and Thorn (1957)
BAL	Current, Hales, and Dobyns (1960)
*Carbimazole	—
Carbutamide	Brown and Solomon (1956)
Chlorpropamide	See above
Cobaltous chloride	Robey, Veazey, and Crawford (1956); Roche and Layrisse (1956)
*Cortisone	Hill, Reiss, Forsham, and Thorn (1950); Berson and Yalow (1952) (also lowers PBI concentration by haemodilution — Blomstedt and Einhorn, 1967)
Cyanide	Hardy, Jeffries, Wasserman, and Waddell (1950)

2, 4-D	Florsheim and Velcoff (1962)
DOCA	Zingg and Perry (1953)
*Hydrocortisone	Danowski *et al* (1962)
*Lithium carbonate	Sedvall *et al* (1968)
*Methimazole	See Wilber and Odell (1965)
*Methylthiouracil	—
*Oxyphenbutazone	Wayne *et al* (1964)
*PAB	Goodwin, Miller, and Wayne (1949)
*PAS	MacGregor and Somner (1954); Munkner (1965)
*Parabromdylamine maleate	Sharpe (1961)
Phenindione	Williams and Doniach (1961); Stewart and Grayson (1966)
Phenylbutazone	Lüllmann (1962)
*Prednisolone	Sherer and Siefring (1956); Wikholm and Einhorn (1963)
*Prednisone	Sherer and Siefring (1956)
Progesterone	Zingg and Perry (1953)
*Propylthiouracil	—
*Resorcinol	Bull and Fraser (1950); Doniach and Fraser (1950)
Salicylate	Good, Potter, and Hetzel (1965)
Sulphonamides	Milne and Greer (1962)
Sulphonyl urea drugs	See chlorpropamide
Thalidomide	Murdoch and Campbell (1958)
Thiopentone	Wase, Repplinger, and Foster (1953)
*Thiouracil and related compounds	2/m
Tolbutamide	Brown and Solomon (1956)
U-9189	Ingbar (1961b)
Vitamin A	Danowski, Wirth, Black, Barton, and Bastiani (1955); Logan (1957); Benedek (1962)
Other Antithyroid Substances	
^{131}I in high dosage	—
^{125}I in high dosage	Greig, Smith, Gillespie, Thomson, and McGirr (1969)

DRUGS AFFECTING THYROXINE-BINDING CAPACITY OF SERUM

Drugs may affect the serum PBI as a result of interference with its thyroxine-binding properties. They may increase the serum PBI as a result of increasing the level of circulating TBG. Alternatively, they may reduce the serum PBI as a result of decreasing the level of circulating TBG or TBPA or as a result of competing with T_4 for TBG. Changes in the level of circulating TBG or TBPA are presumed to arise from drug-induced alterations in their rates of synthesis by the liver. The effects of drugs are given in Tables I-V.

Drug	*Reference*
*Androgens (including 'anabolic' steroids)[1]	
Eg, methyltestosterone, norethandrolone, oxymetholone, testosterone	See Keitel and Sherer (1957); Federman *et al* (1958); Engbring and Engstrom (1959); Braverman and Ingbar (1967); Rosin and Farran (1968)
*Norethynodrel	Winikoff (1968)
*Oestrogens	
Eg, diethylstilboestrol, ethinyloestradiol, oestradiol, oestrone	See Engstrom, Markardt, and Liebman (1952); Feldman and Danowski (1956); Dowling *et al* (1956b); Engbring and Engstrom (1959); Dowling, Freinkel, and Ingbar (1960a); Alexander and Marmorston (1961); Hollander, Garcia, Sturgis, and Selenkow (1963); Fisher, Oddie, and Epperson (1966)
Oral contraceptives containing oestrogens The oestrogenic constituents are responsible. The progestogenic constituents, other than norethynodrel, have no effect on PBI (Winikoff, 1968)	
*Perphenazine	See Oltman and Friedman (1963); Cranswick and Simpson (1963 and 1964) but iodinated contaminants may be present in the formulation (Hansen and Siersbaek-Nielsen, 1967)

Table I *Drugs which may decrease the serum PBI level by lowering the concentration of circulating TBG*

[1]Methylandrostenolone does not affect the PBI (Danowski *et al* 1965).

Table II *Drugs increasing serum PBI level by raising concentration of circulating TBG*

Drug	*Reference*
Adrenaline	Korst and Beierwaltes (1956);
Animal experiments suggest that adrenaline causes release of PBI from the thyroid	(Botkin and Jensen, 1952; Ackerman and Arons, 1958)
Chlorpromazine	Reichlin, Koussa, and Witt (1959)
Evan's blue	Yamada, Whallon, Tomizawa, Shimoda, and Schichijo (1965)
*Hydrochlorothiazide	Mehbod *et al* (1967)
Niagara sky blue	Yamada *et al* (1965)
Niagara sky blue G.B.	Yamada *et al* (1965)
Trypan blue	Yamada *et al* (1965)

Table III *Drugs decreasing serum PBI by unknown means*

Drug	*Reference*
*Deseril (= lysergic acid butanolamide)	
*Ether (anesthesia) causes mobilization of PBI stores	Fore, Kohler, and Wynn (1966)
Fluoropyrimidines	Blomgren and Ansfield (1965)
Insulin	
Possibly stimulates TSH release	Sendrail *et al* (1966)
Lysergic acid butanolamide	
In rats stimulates TSH release and has variable action on thyroid ^{131}I uptake	Mess and Szántó (1964); Szántó and Reviczky (1966)
Nialamide	
Variable effect on thyroid ^{131}I uptake in rats	Szántó, Reviczky, and Grynaeus (1964)
Pyrazinamide	De Simoni (1957)
Vasopressin	
Stimulates thyroid ^{131}I release	Garcia, Harris, and Schindler (1964)

Table IV *Drugs increasing serum PBI by unknown means*

Drug	*Reference*
*BHDB	Escobar del Rey and Morreale de Escobar (1962)
Butyl-4-hydroxy-3:5-di-iodobenzoate (= BHDB)	
2,2(4-chlorophenyl,2-chlorophenyl) 1,1-dichloroethane (= Op'DDD)	
DNP (= 2:4-dinitrophenol)	
*Dilantin (= diphenylhydantoin)	
2:4-Dinitrophenol	Wolff, Standaert, and Rall (1961); Morreale de Escobar and Escobar del Rey (1961a and b)
*Diphenylhydantoin (long-term therapy)	Wolff *et al* (1961); Lightfoot and Christian (1966) Chin and Schussler (1968). Acute treatment is without effect (Levy and Marshall, 1964)
Gentisate	Woeber and Ingbar (1964)
Op'DDD	Danowski, Sarver, Moses, and Bonessi (1964); Marshall and Tompkins (1968)
γ-Resorcylate	Woeber and Ingbar (1964); Good *et al* (1965)
Salicylates	Austen *et al* (1958); Christensen (1959); Wolff *et al* (1961); Good *et al* (1965)

Table V *Drugs decreasing serum PBI by competing with T_4 for TBG or TBPA*

Appendix II

Drugs Reported not to Cause Changes in the Serum PBI Level

Drug	*Reference*
Acetazolamide	Schteingart *et al* (1960)
Amphenidone	Pittman (1962)
Atromid (= clofibrate)	
Busulphan	Vivacqua, Haurani, and Erslev (1967)
Calcium	Harrison, Harden, and Alexander (1967)
Chorionic gonadotropin	Craig *et al* (1963). Average increase of 0·6 μg/100 ml not statistically significant
Chlormadinone	Winikoff (1968)
Chlorphenindione	Stewart and Grayson (1966)
Clofibrate	Harrison and Harden (1966) found no effect on serum PBI Chang, Pinson, and Malone (1967) found reduced TBPA capacity but normal TBG capacity
Clomiphene	Cushman, Alter, and Hilton (1965)
Cyclopropane (anaesthesia)	Fore *et al* (1966)
Digitoxin	Danowski *et al* (1965)
Dimethisterone	Winikoff (1968)
Ethisterone	Winikoff (1968)
G 25671 (phenylbutazone analogue)	Linsk, Paton, Persky, Isaacs, and Kupperman (1957)
Halothane (anaesthesia)	Fore *et al* (1966)
Hydrochlorothiazide	Schteingart *et al* (1960)
Insidon (= opipranol)	
Medroxyprogesterone	(In contraceptive preparations, Hollander *et al*, 1963; Winikoff, 1968.) A large dose given to suppress the pituitary in precocious puberty has caused hypothyroidism (Hubble, 1963)
Megestrol	Winikoff (1968)
1-Methyl-Δ^1-androstenolone	Danowski *et al* (1965)
Metronidazole	Harden, Chisholm, and Cant (1967)
Nicoumalone	Stewart and Grayson (1966)
Nitrous oxide (anaesthesia)	Fore *et al* (1966)
Norethisterone	Winikoff (1968)
Opipranol	Bourquin (1967)
Pontocaine	Fore *et al* (1966)
Propranolol	Krikler (1966)
Schiller's solution (cervical smears)	Braverman *et al* (1968)
Surital	Fore *et al* (1966)
Tetracycline	Becker, Katz, and Miale (1967)
Thiopentone (anaesthesia)	Fore *et al* (1966)
Thioridazine	Taubert, Haskins, and Moszkowski (1966)
Warfarin	Stewart and Grayson (1966)