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Endemic Goitre in Eastern New Guinea

With Special Reference to the Use of Iodized Oil in Prophylaxis and Treatment

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Previous surveys having indicated a high goitre endemicity in the mountainous Huon peninsula of eastern New Guinea, a study was carried out in 1964 which indicated severe iodine deficiency in the inhabitants of the area; trials were undertaken to determine whether the injection of iodized oil would correct that deficiency and what effect injections given in previous years had had.

The results showed that, whereas the urinary iodine and ^{131}I uptake in New Guineans who had received iodized oil in 1957 were similar to those in untreated persons, yet a single 4-ml injection (2.15 g iodine) of iodized oil appeared substantially to correct iodine deficiency for 4-5 years. There was also a significant regression of goitre in 60 of 61 persons with easily visible goitres within 3 months of their receiving an injection. No case of thyrotoxicosis or iodism was seen in more than 2000 persons who were given injections.

The authors recommend the injection of iodized oil particularly for the correction of iodine deficiency in children and in women of child-bearing age whenever the efficacy of other measures is uncertain. The method is relatively inexpensive and well suited to mass prophylaxis among people with a low standard of living.

INTRODUCTION

Endemic goitre has been known to occur in New Guinea for many years. Kelly & Snedden (1960) described a patchy distribution of endemic goitre throughout the highly mountainous island. In the Australian Territory of Papua and New Guinea (Eastern New Guinea) surveys have been carried out from time to time by medical officers, with reports filed in the Department of Public Health. Particular attention has been paid to the Huon Peninsula as one representative area showing a high prevalence (McCullagh, 1963a; Hennessy, 1964).

In the belief that endemic goitre, though not necessarily caused by iodine deficiency, could be successfully treated with iodine, and in view of the great difficulties that would be encountered with salt iodization in an area where virtually no salt is consumed, iodized oil (Neo-Hydriol, May & Baker) was introduced as a therapeutic measure by McCullagh in 1957. He examined 10 252 indigenous persons in the area, and of these selected 7881, who were either non-goitrous or had only small goitres, as suitable for medication; 3934 were given an intradeltoid injection of oil, and 3947 were given a similar injection of normal saline solution to form a control group (McCullagh, 1963a).

Subsequently, McCullagh in 1960 and Hennessy in 1962 found that goitre was less prevalent in New Guineans who had received oil than in untreated persons in the control group. In his report, Hennessy (1964) stated that the visible goitre rate (VGR) was 1.8% in the treated female group (1260 examined) compared with 10.0% in the untreated female group (1235 examined). The differences for VGR in males were less marked—0.5% in the treated group (1160 examined) and 3.5% in the untreated group (1196 examined). In 1964 the present investigation was undertaken to determine whether untreated New Guineans were deficient in iodine, and whether iodized oil could correct the deficiency.

Description of the area

Fig. 1 shows (dots) the known goitrous areas in New Guinea. Studies in the Mulia area of

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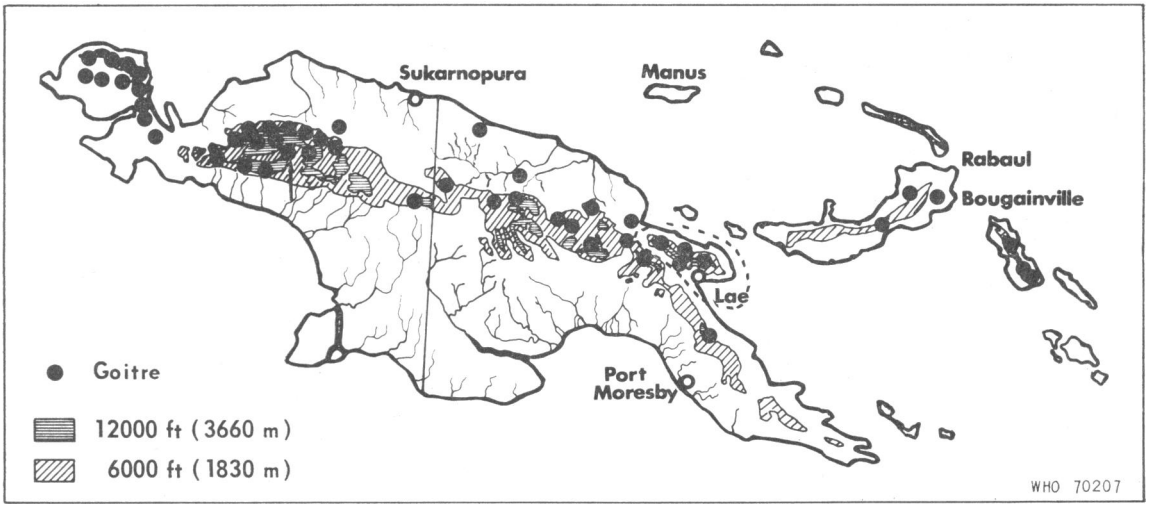
FIG. 1
KNOWN AREAS OF ENDEMIC GOITRE IN NEW GUINEA [a]



[a] The Huon peninsula is north of Lae in eastern New Guinea; the Mulia area is in the centre of West Irian.

West Irian have been previously reported by Choufoer et al. (1963). The area concerned in the present survey is shown, within the broken line, directly north of Lae: it includes the Wain and Naba census divisions of the Morobe subdistrict. These areas, of 205 and 212 square miles (530 km² and 550 km²) respectively, lie in the lower slopes of the rugged Saruwaged Mountains. The 28 Wain and 32 Naba villages visited were found at heights of between 1500 and 6000 feet (ca 450 m-1830 m). To the north are the uninhabited peaks of the Saruwaged Mountains, which rise to 12 000 feet (over 3600 m), while to the south is the valley of the Markham River and the coastal region of Lae. The total population of the two areas is approximately 15 000; the people live in villages of between 100 and 500 each, scattered throughout the area (Fig. 2).

The Wain villages are within four hours' walking distance of Boana, where there is a Lutheran Mission, but one or two days' walk is needed to reach those of the Naba. The mountains are covered with a thick growth of tropical rain-forest so that to travel from one village to the next it is necessary to walk along paths or roads cut through the undergrowth and along the sides of mountains. The distance between villages varies between 15 minutes' to four hours' walking time.

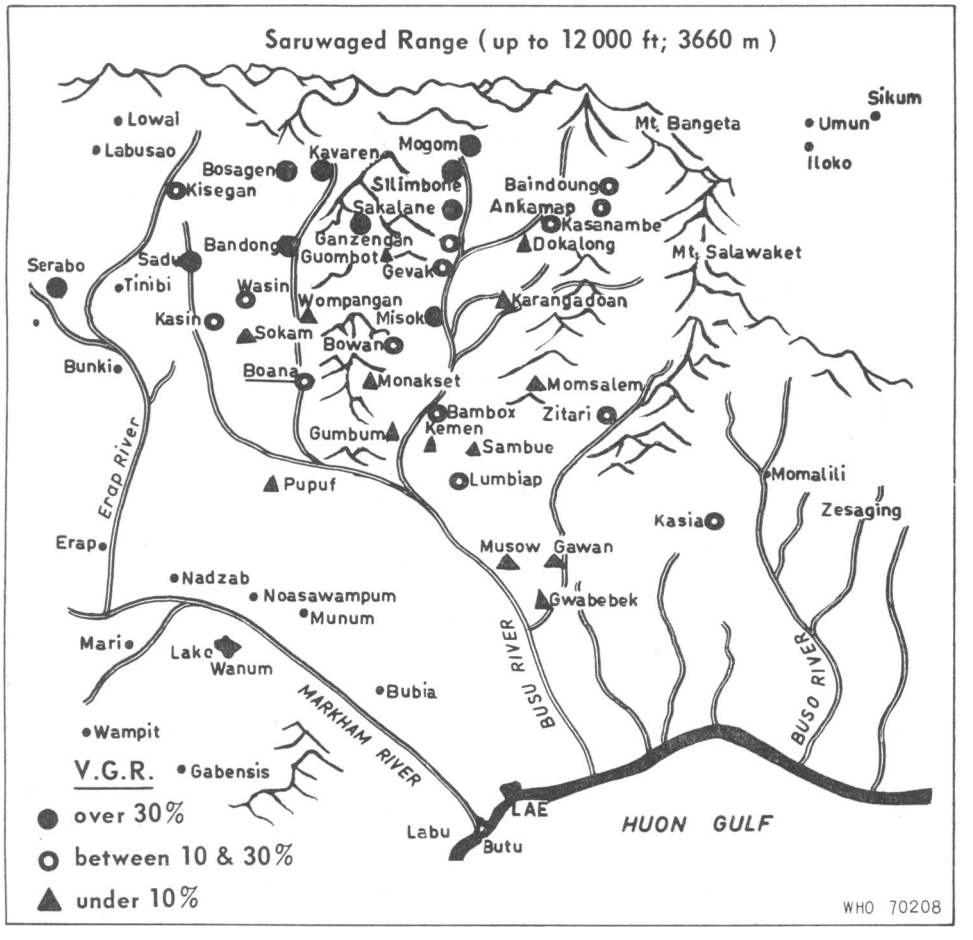
The people have remained isolated partly because of topographical difficulties, partly because of shyness and partly because of continual warfare between the neighbouring villages and with the people of coastal areas until very recent times. Villages usually were found near the crest of steep mountain ridges where in pre-contact times there was protection and adequate warning of an attacking force. The climate is tropical, with extremes of temperature, varying between warm and humid during the day and extremely cold at night—pneumonia is very common.

The people

The indigenes are dark-skinned, short, muscular and rarely, if ever, obese. Their diet consists largely of sweet potato (with only 2%-3% protein content) with occasional fruit and European types of vegetables. Meat, consisting of native pig, is eaten only rarely on festival occasions, which may occur only once or twice a year. Almost all the food eaten, except for an occasional tin of meat or fish, is grown within the area.

Little is known of the origin of the people, and one can only guess at the forces which led them to migrate from the coast where food is plentiful to such inhospitable mountains where food is hard to obtain, and every piece of arable land is now cultivated. Presumably war and disease were the dominant forces in their migration. The length of

FIG. 2
RIVERS AND INDIVIDUAL VILLAGES IN HUON PENINSULA



time these people have been in the mountains is unknown.

With the arrival of the missionaries (two Lutherans, Mr & Mrs Bergman, who are still at Boana today), peace and relative prosperity came to the area. The inhabitants began to grow the now flourishing fruit and vegetables introduced by the missionaries and they have also begun to raise sheep and cattle successfully. The missionary influence is much in evidence and the people are devout Christians. The main source of income is coffee, which is now being grown and processed by the people themselves with periodic advice from the missionaries and Government officers, who also supervise health and hygiene and settle disputes.

It became obvious that there was a continual migration of people so that there is no real evidence of genetic isolation. Because of the difficulty of the terrain the population is very remote from modern civilization, although only some 25 miles (40 km) from Lae. Less than one tin of meat per family per year is imported into the area and much of that is consumed by the semi-permanent New Guinean residents of Boana. The villagers prefer to spend their modest incomes on clothes, knives, kerosene and lanterns.

The Wain and Naba groups are separated largely by language differences, but the common language is pidgin English by means of which communication with Europeans is possible. The names of each per-

son and his year of birth have been entered into census books and these books are revised annually. Some difficulty was encountered, however, in accurate identification as each person has many names, only one of which may be entered into the census book. It was therefore virtually impossible to obtain 100% accuracy in determining to which treatment group any one individual belonged, but over-all it was possible to obtain satisfactory evaluation.

The co-operation of the villagers was, as a rule, good, although the people of the Naba were a little shy and slower to help. They were, however, very much pleased at the help that was being given them, and it was usually possible to obtain volunteers for experiments in the villages.

Goitre was obviously a scourge in this area and many social barriers had been built up around the goitrous people. It was certain that large goitres were a bar to marriage and large goitres also interfered with neck and head movements, making work in the gardens difficult. However, it did appear that, apart from the discomfort, few complications directly referable to the lump in the neck occurred. The New Guineans considered both the goitre and the mentally defective people, who have been classified as endemic cretins, a great nuisance and they were keen for preventive and curative measures to be undertaken.

MATERIALS AND METHODS

One of the authors (I.H.B.) led a field team consisting of a European technical assistant, two New Guinean medical orderlies and two New Guinean houseboys. This group stayed in a village for between one and five days, during which time all members of the village were examined for goitre. In a number of villages blood and urine samples were collected and despatched by runner to Boana and thence by air nearly 3000 miles (4800 km) to the laboratory of the University Department of Medicine at The Queen Elizabeth Hospital in Adelaide, South Australia. Volunteers were also found who were given oral tracer doses of radioactive iodine (^{131}I) for estimations of thyroid uptake. Observations were also carried out on a group of coastal villagers receiving a semi-European style of diet while employed as medical orderlies of the ANGAU Memorial Hospital, Lae, as well as on a group of normal subjects in Adelaide, South Australia.

Clinical assessment

Villagers were examined for goitre by families when their names were called from the village census book. Assessment of thyroid size was by the method of Perez et al. (1960):

Size 0: normal gland.

Size 1: palpable but not visibly enlarged.

Size 2: visibly enlarged.

Size 3: persons with very large goitres.

The results were expressed as the visible goitre rate (VGR), which was the percentage of people with thyroid size 2 or 3.

The thyroid size together with age and sex was recorded on worksheets without reference to previous records. Reproducibility was checked in one village of 250 persons, with two estimates three months apart. Figures of 41% and 39% for visible goitre rate (sizes 2 and 3) were obtained; this was considered satisfactory.

^{131}I uptake data

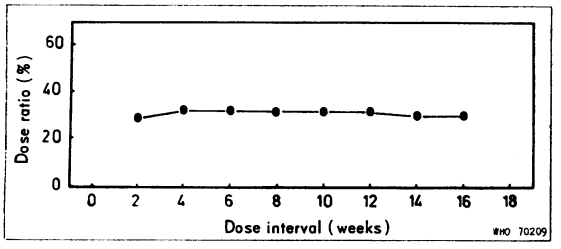
^{131}I in 10 μCi doses was given to the fasting patient and the uptake was calculated at 3 and 24 hours. Subjects were of either sex, over 14 years of age, with size 2 or no visible goitre. No observations were made on size 3 goitres because of unsatisfactory geometry preventing accurate counting.

The counting equipment consisted of a transistorized portable scaler (Nuclear Enterprises, Edinburgh) powered from a 6-volt battery, and a 1¾-in × ½-in (ca 44 mm × 12.5 mm) thallium-activated sodium-iodide crystal with photomultiplier; the crystal was shielded with a 40-lb (18-kg) lead collimator of standard design. Results were expressed as percentage uptake, and a correction factor of 0.85 was obtained by the method of Stanbury et al. (1954).

A check for the consistency of the equipment was made by calculating the ratio of the standard 2 weeks old to the new standard and satisfactory results are shown in Fig. 3.

Perchlorate discharge tests were performed by giving a dose of ^{131}I to fasting patients and recording the uptake at 2 hours. Then 1000 mg of potassium perchlorate were administered orally and the uptake again measured an hour later. A fall of greater than 5% was required for an abnormal result (Baschieri et al., 1963).

FIG. 3
RESULTS OF SERIAL MEASUREMENTS OF STANDARD DOSES OF ^{131}I AT 2-WEEK INTERVALS



Blood samples

Blood was collected in 30-ml iodine-free vacuum Venules and then dispatched untouched to the laboratory. This minimized the possibility of infection, which would probably have occurred if separation had been attempted in the field. Satisfactory separation of serum was achieved with the exception of a few haemolysed samples, which were discarded.

The following determinations were carried out on the serum:

Protein-bound iodine (PBI). This was measured by the method of Acland (1957).

T_3 resin uptake. A modification of the method of Woldring et al. (1961) was used. The results were expressed as a percentage of a pooled serum standard.

Serum iodine-containing amino-acids. These were also studied, using previously described chromatographic procedures (Wellby, 1962).

Serum total protein. The method used was that of Reinhold as described by Varley (1962).

Urine samples

Twenty-four-hour urine samples were collected in washed polyethylene flasks and measured, and a 60-ml aliquot was transferred to a 2-fluid-ounce (56-ml) bottle with thymol in toluene as a preservative. Co-operation in collection was usually good, and the samples were believed to be true 24-hour specimens. Samples of less than 300 ml were discarded although there was good reason to believe that some genuine 24-hour specimens were of less than 300 ml.

The aliquots were flown to the laboratory in Adelaide for the following investigations:

24-Hour urinary iodine. The iodine was measured using the method for plasma PBI determination, following the addition of a measured quantity of pooled serum to the urine specimens as described by De Visscher et al. (1961).

Urinary creatinine. This was estimated colorimetrically by the Jaffe reaction (Varley, 1962).

Urine sodium and potassium. These were determined by the standard methods using an Eel flame photometer.

Urinary total nitrogen. This was measured by a semi-micro-Kjeldahl method.

Drinking water

Twenty-three samples of drinking water were collected and then concentrated in the laboratory by evaporation. The iodine content was measured by the method used for urinary iodine.

STUDIES OF IODINE NUTRITION

Clinical data

Of a total population of 14 500 in the Wain and Naba divisions, 10 109 persons were examined for goitre. The absentee rate of 31% was due to the fact that many of the young men and their families were working in Lae or on plantations, while many children were at schools and could not be found. A total of 1807 persons had a visible goitre, making the VGR for the area 18%.

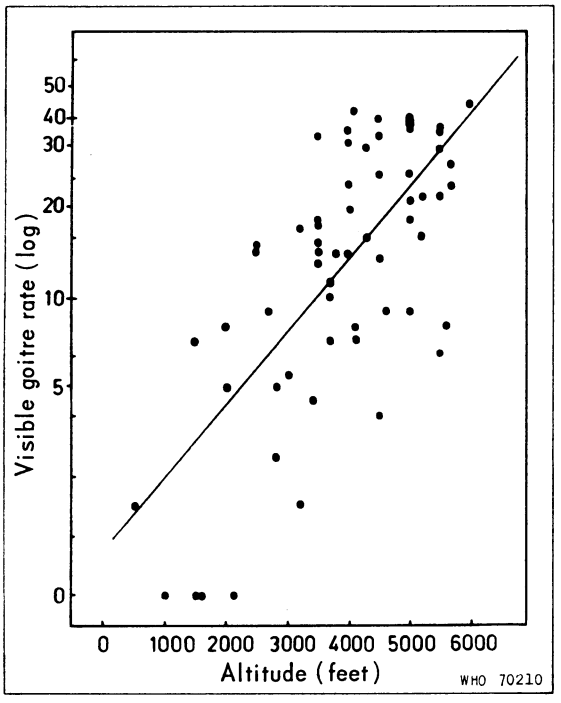
A scatter diagram (Fig. 4) shows altitude plotted against log VGR. The regression line obtained was highly significant ($P<0.001$), showing a direct relation between elevation and the VGR of the population. There was a wide range of results, which was expected since the population of any village received vegetables from a large area. The villages were taken from more than one mountain, so that the VGR of a village at a certain altitude on one mountain need not necessarily reflect the VGR of a village at the same level on another mountain.

Although no evidence for any hereditary factor has been produced, it was observed, in examination by families, that there was a familial tendency for goitre development throughout the area.

Physical examination of 400 patients on whom ^{131}I-uptake studies were done revealed no clinical evidence of hyperthyroidism or hypothyroidism.

Blood-pressure levels were between 100 mm Hg and 110 mm Hg systolic and 70 mm Hg and 80 mm Hg

FIG. 4
RELATION BETWEEN VISIBLE GOITRE RATE IN INDIVIDUAL VILLAGES AND ALTITUDE[a]



[a] 1000 ft ≃ 305 m.

diastolic. This is considered normal for New Guineans. Dentition was normal, while a few persons had other abnormalities such as old fractures with malunion. The spleen was enlarged in some cases, but the liver was not usually palpable.

Obesity was rare, and the whole population was short in stature, but only one case of classical sporadic cretinism was seen. This was in a 1-year-old baby who died within a month of our visit.

At higher altitudes, pneumonia, chronic sinusitis and chronic chest infection were common. At lower levels, malaria became more common so that large spleens were more often felt.

While the thyroid glands were enlarged in 18% of the population, with females predominating, no cases of carcinoma of the thyroid gland were recognized, and only three persons were found who had signs of airway obstruction.

In many people, however, the thyroid gland was so enlarged as to cause discomfort, even to the extent that head movements were impaired, making work difficult. The exact morbidity due to mechanical discomfort by the goitre was impossible to assess, as the people did not readily give medical histories. They also had had these swellings for many years and could not remember anything else.

Laboratory data

Urinary iodine. There was a significant difference between the mean for the whole population (11.5 μg/24 h ± 12.4 μg/24 h) and the mean for coastal villagers at Lae which was 49 μg/24 h ± 55 μg/24 h. No significant difference was observed between high and low villages (Table 1).

The figures in Table 1 also show that the goitrous group (mean 6.7 μg/24 h ± 7.1 μg/24 h) is significantly different from the non-goitrous group (mean 13 μg/24 h ± 13.3 μg/24 h).

Fig. 5 shows the urinary iodine values in untreated persons in the endemic area (saline injected and untreated are the same for the purposes of the experiment) compared with Adelaide and New Guinea coastal groups. The data indicate that both New

FIG. 5
URINARY IODINE DETERMINATIONS IN UNTREATED HIGHLAND NEW GUINEANS COMPARED WITH COASTAL NEW GUINEANS AND NORMAL SUBJECTS IN ADELAIDE, AUSTRALIA

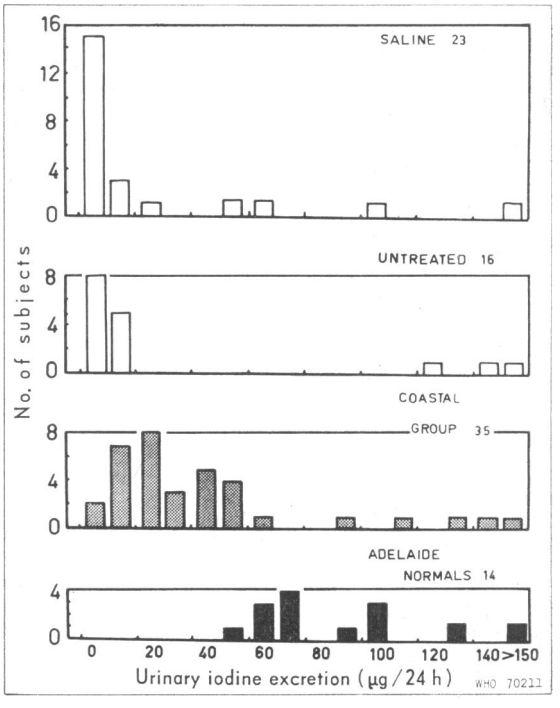


TABLE 1
THYROID FUNCTION IN NEW GUINEA SUBJECTS

Group	Urinary iodine (μg/24 h)	^{131}I-uptake (% at 24 h)	Serum PBI (μg/100 ml)	T_3 resin uptake (% of normal)
Endemic area	11.5***±12.4 (91)	70** ±19 (181)	4.1***±2.1 (204)	91.0 ±12.1 (195)
Coastal	49 ±55.0 (31)	60 ±17 (19)	6.0 ±0.9 (19)	95.9 ±11.4 (19)
High villages in endemic area	11.2 ±12.0 (44)	68 ±22 (58)	4.4** ±2.2 (59)	88.0***±11.9 (58)
Low villages in endemic area	16.2 ±15.1 (25)	66 ±16 (64)	5.3 ±1.6 (60)	102.1 ±15.8 (57)
Goitrous in endemic area	6.7** ± 7.1 (22)	77***±13 (59)	2.9***±1.7 (85)	86.2***±14.7 (80)
Non-goitrous in endemic area	13 ±13.3 (69)	67 ±20 (122)	4.9 ±2.0 (119)	94.0 ±17.9 (115)
Australian normal range	70—140	16—40	3.6—7.2	70—110

**: P<0.01 } using *t*-test for comparison of endemic area and coastal New Guinean villagers or goitrous and non-goitrous subjects. The figures given are for the mean ± the standard deviation, with the number of subjects tested shown in parentheses.
***: P<0.001 }

Guinea groups were iodine-deficient when compared with normal subjects in Adelaide.

Stable iodine in water. Twenty-three samples of water were collected from the experimental area at various altitudes. The mean value of stable iodine in water was 0.4 μg/litre ± 0.2 μg/litre in the area examined. One village at the lower end of the Wain had a value of 4.6 μg/litre and a sample collected at Lae showed 2.4 μg/litre.

Values for Adelaide were found to be 19.1 μg/litre, while distilled water gave a value of 0.5 μg/litre and iodine-free water from the laboratory gave a value of 0.1 μg/litre.

Radioactive iodine studies. There is a significant difference ($P<0.01$) between all the endemic area villagers (mean 70% ± 19%) and the coastal villagers (mean 60% ± 17%), who are at sea-level eating a semi-European diet. High villages do not show any significant difference when compared with the low villages (Table 1).

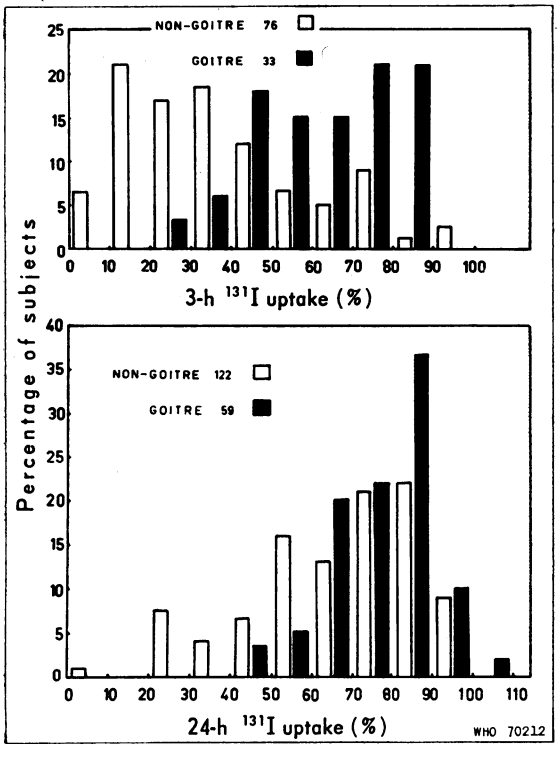
There is a highly significant difference ($P<0.001$) between goitrous (mean 77% ± 13%) and non-goitrous persons (mean 67% ± 20%) as shown in Fig. 6. The 3-hour values were observed in New Guineans who had fasted overnight prior to the administration, in the morning, of the tracer dose. These readings show a highly significant difference ($P<0.001$) between goitrous and non-goitrous groups (Fig. 6), the goitrous group having the higher figure. The mean values obtained in the 3-hour and 24-hour readings were above normal.

Fig. 7 shows 24-hour ^{131}I-uptake figures in the three control areas—two low-VGR villages (VGR 0 and 4%) at 1000 feet (300 m) or less, and the coastal group at Lae. All these were elevated, suggesting iodine deficiency in these groups as well.

Serum protein-bound iodine. The results are set out in Table 1. A total of 223 estimations were performed on sera of untreated subjects. The mean PBI for the endemic area population studied was 4.1 μg/100 ml ± 2.1 μg/100 ml. A significant difference ($P<0.001$) was found between the mean for all

FIG. 6

3-HOUR AND 24-HOUR ^{131}I UPTAKES IN GOITROUS AND NON-GOITROUS NEW GUINEANS IN THE ENDEMIC AREA



untreated New Guineans and the mean for the group of coastal villagers on a semi-European diet (mean 6.0 μg/100 ml $\pm$ 0.9 μg/100 ml).

Goitrous persons had a mean PBI of 2.9 μg/100 ml $\pm$ 1.7 μg/100 ml, which was significantly lower ($P<0.001$) than that of non-goitrous persons (mean 4.9 μg/100 ml $\pm$ 2.0 μg/100 ml) (Fig. 8). The mean was below our laboratory's accepted lower limit of normal of 3.6 μg/100 ml.

Non-goitrous New Guineans living at higher altitudes (and from villages with a VGR greater than 10%) had a serum PBI of 4.4 μg/100 ml $\pm$ 2.2 μg/100 ml. This was significantly lower ($P<0.0125$) than values for those who were living at lower levels and in villages with a VGR of less than 10% (mean 5.3 μg/100 ml $\pm$ 1.6 μg/100 ml).

T_3 resin uptake. A difference was observed between the mean for the whole endemic area (mean 91.0% $\pm$ 12.1%) and the control group of coastal villagers in Lae at sea level (95.9% $\pm$ 11.4%).

There was a significant difference within the endemic area between the goitrous (mean 86.2% $\pm$ 14.7%) and the non-goitrous group, which has a mean of 94.0% $\pm$ 17.9%. A significant difference was also demonstrated between subjects from high villages (mean 88.0% $\pm$ 11.9%) and those from low villages (mean 102.1% $\pm$ 15.8%).

It was apparent that none of these groups fell into the hypothyroid range, although some of the goitrous patients had values below normal.

Discussion

Measurements of urinary iodine excretion have been made in many endemic goitre surveys and have been found to be low in nearly all cases. Some 24-hour urinary figures obtained include

FIG. 7

24-HOUR ^{131}I UPTAKES IN TWO VILLAGES WITH LOW VISIBLE GOITRE RATES AND IN COASTAL GROUP

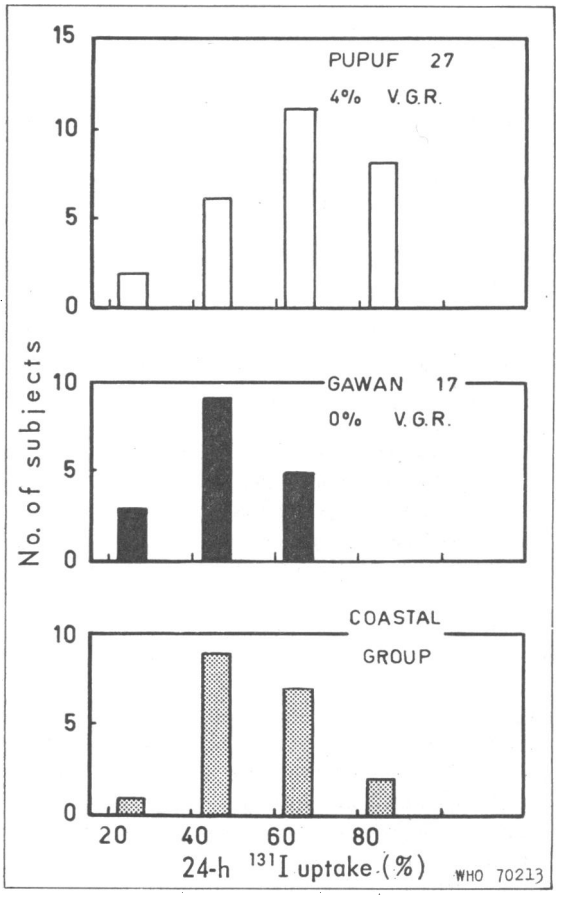
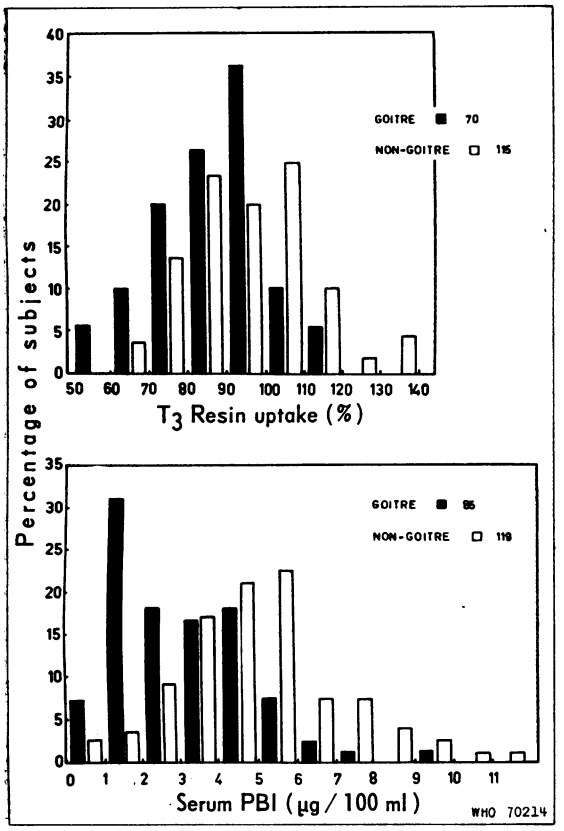


FIG. 8

SERUM PBI AND SERUM T_3 RESIN UPTAKE IN GOITROUS AND NON-GOITROUS NEW GUINEANS IN THE ENDEMIC AREA



23 μg in Argentina (Stanbury et al., 1954), 18 μg $\pm$ 14 μg in Venezuela (Roche et al., 1957), 49.1 μg in Finland (Lamberg et al., 1958), 18.7 μg $\pm$ 6.9 μg in the Democratic Republic of the Congo (De Visscher et al., 1961), and less than 10 μg in the Himalayas (Ramalingaswami et al., 1961). The latest 24-hour figures reported in West Irian by Choufoer et al. (1963) are 4.1 μg $\pm$ 0.3 μg and 2.6 μg $\pm$ 0.2 μg. Fig. 9 shows the urinary iodine expressed per gram of creatinine from the various areas including the Huon peninsula, and the coastal group in Lae, compared with Adelaide normal subjects and people living in Tasmania and Venezuela. Compared with Follis' data (1964a), derived from various endemic areas in the world, the Huon peninsula had a very low urine iodine. The coastal-village group was also low by these standards.

From the work of the foregoing authors and others it would appear that the normal daily urinary iodine excretion should be greater than 75 μg/24 h to 100 μg/24 h. The normal for our laboratory was found to be greater than 70 μg/24 h.

There is no doubt that, when comparing the urinary iodine figures quoted from other goitrous areas, the values found in the Huon peninsula (11.5 μg/24 h $\pm$ 12.4 μg/24 h) indicate severe iodine deficiency. The significant difference between the goitrous and non-goitrous persons is due in part to the altitude distribution of the goitrous and possibly to the fact that young men move more freely to and from towns and may be relatively more sophisticated in their diets than the women, while the women more commonly have goitre than men.

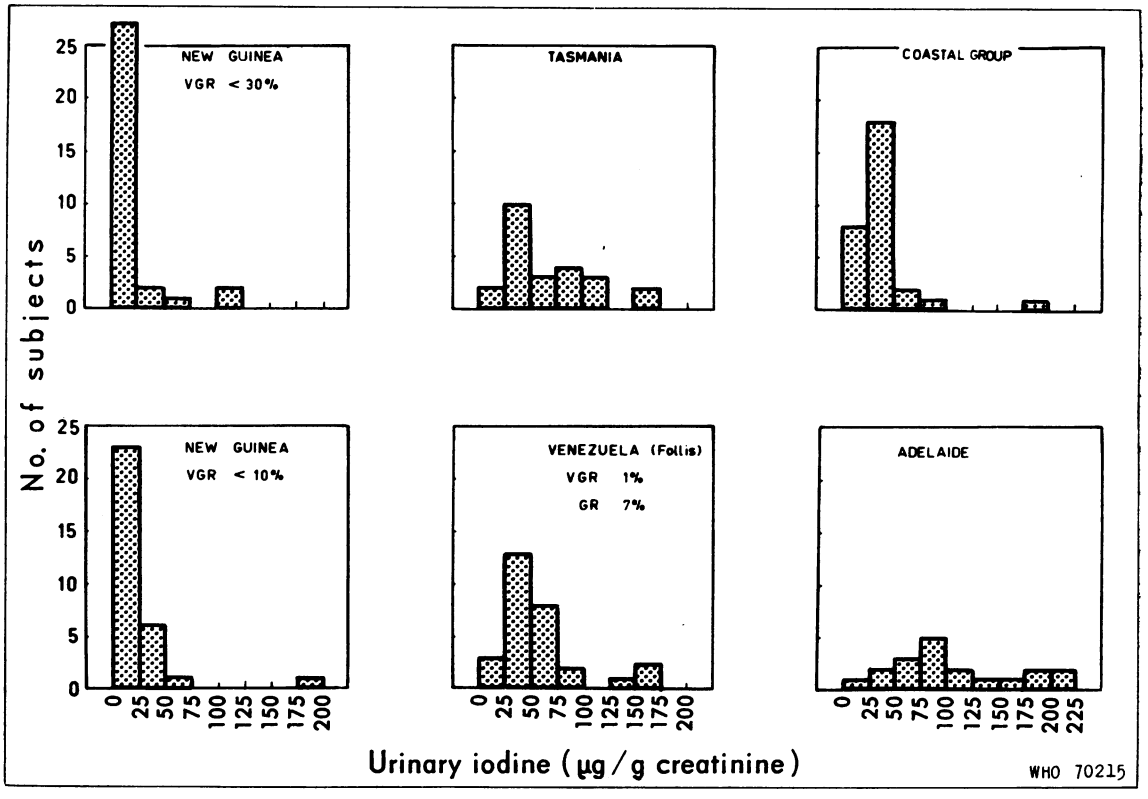
It is also of interest that New Guineans at sea level, eating semi-European diets, were below normal in their urinary iodine excretions, suggesting iodine deficiency. This possibility was confirmed by radioactive iodine data.

The radioactive iodine data suggest that goitrous glands are more efficient in trapping a tracer dose of radioactive iodine and therefore more able to take up dietary iodine. The 3-hour figures indicate that iodine is trapped earlier in goitrous glands so that less iodine is presented to the kidneys for excretion. Stanbury et al. (1954) have shown that there is no adaptation by the kidney to iodine deficiency.

That there is no difference between radioactive iodine uptake figures in non-goitrous patients from high and low villages probably indicates that in the area studied, even at low altitudes and in villages of low VGR, the thyroid is at its peak efficiency in taking up ^{131}I. However, the coastal villagers show lower radioactive iodine uptakes than those in the goitrous areas, indicating that these uptakes are not maximal. Lack of correlation between high and low villages in ^{131}I-uptake studies may also indicate that this test is rather less sensitive than has hitherto been suspected.

High ^{131}I-uptake figures have previously been reported by many (Stanbury et al., 1954; Roche et al., 1957; Choufoer et al., 1963) and previous workers have been able to demonstrate a correlation between radioactive iodine uptake studies and the urinary excretion of stable iodine (Stanbury, 1954; Follis, 1964b). In the Huon peninsula the stable urinary iodine was low in both high and low villages, with no significant difference between them, although there was some difference in the means.

FIG. 9
URINARY IODINE DETERMINATIONS IN THE VARIOUS NEW GUINEA GROUPS AND IN AUSTRALIA AND VENEZUELA



There was no correlation here between ^{131}I uptake and urinary iodine, as the uptakes were maximal and the urinary iodine levels were minimal.

In many goitrous areas of the world, the serum PBI has been found to lie within normal limits (Stanbury et al., 1964; Lamberg et al., 1962) while Parker & Beierwaltes (1962) found elevated levels in the pupils of a school for retarded children who had been iodine-deficient for 10 years.

In the Democratic Republic of the Congo (Ermans et al., 1961) and in the Himalayas (Ramalingaswami et al., 1961) protein-bound iodine levels have been found to be below normal, without evidence of clinical hypothyroidism. Choufoer et al. (1963) reported a similar phenomenon in Mulia and suggested that the low protein diet may be responsible for masking clinical hypothyroidism. In the Huon peninsula the goitrous New Guineans had a mean PBI (and free thyroxine) which was in the range of hypothyroidism and which was significantly lower than levels in non-goitrous New Guineans. A significant difference was also found in the serum PBI between non-goitrous persons living in high and in low villages and between the mean serum PBI for the endemic area and that for the coastal villagers, the latter being were within the normal range.

The T_3-resin-uptake results followed closely the trend of the PBI levels; however, none of the means was in the hypothyroid range, although a few individual samples were below the normal range for goitrous persons. Calculation of the free thyroxine index also indicated low values (Buttfield et al., 1966).

No obvious explanation is apparent for the fact that none of the New Guineans examined showed any evidence of hypothyroidism, despite serum PBI levels of 0.8 µg/100 ml and 0.9 µg/100 ml being found in the goitrous group.

Apparently these people had been living in the Saruwaged Mountains for some centuries. Choufoer et al. (1965) thought that the infant mortality may be as high as 60% in the first year of life in Mulia. Unofficial reports and our own observations support this figure, although no actual data are available.

It seems likely that, due to rigorous selection of the fittest in this community as the people moved higher into the mountains, the population became genetically adapted (although not completely) to iodine deficiency. Thus they may have been able to survive in very harsh conditions with serum PBI which would most probably have been lethal in non-adapted persons. It is apparent that further studies will be necessary to elucidate the mechanism of adaptation by the iodine-deficient person to low serum levels of thyroid hormone.

It has been commonly believed (De Smet, 1960; Choufoer et al., 1963) that goitre is an adaptation by the thyroid gland to iodine deficiency. From the data presented, however, there appears to be in the goitrous gland a *failure* of adaptation to iodine deficiency. The glands of non-goitrous persons can take up radioactive iodine avidly, maintain a normal plasma protein-bound iodine, and nearly normal free-thyroxine levels. However, the glands of goitrous persons living in exactly the same environment as non-goitrous persons were able to retain iodine more avidly but were less efficient in producing thyroid hormone. This question is discussed more fully elsewhere (Buttfield et al., 1966).

STUDIES OF GENERAL NUTRITION

It seemed reasonable that, since there was a deficiency of one dietary substance, iodine, other substances essential for normal health may also have been deficient. Accordingly, a survey of the main indices of nutrition was carried out, using the blood and urine samples collected for thyroid investigation.

Results

Total serum protein. In Table 2 the values for total serum proteins are given. There is no significant difference between any groups within the experimental area. The values for the coastal group in Lae were also in the same range. All values were within the normal range for Europeans (Varley, 1962). No electrophoretic studies were possible.

TABLE 2

INDICES OF NUTRITION IN NEW GUINEA SUBJECTS

Group	Total serum protein (g/100 ml)	Urinary nitrogen (g/24 h)	Urinary creatinine (g/24 h)	Urinary K^+ (mEq/24 h)	Urinary Na^+ (mEq/24 h)	Urinary iodine (μg/24 h)
Endemic area	6.9±1.2 (280)	2.7***±1.7 (74)	0.6***±0.3 (131)	149***± 80 (131)	32***±35 (131)	11.5***±12.4 (91)
Coastal	5.8±0.5 (17)	6.8 ±5.5 (30)	1.1 ±0.5 (30)	41 ± 39 (30)	77 ±56 (30)	49 ±55.0 (31)
High villages in endemic area	6.9±1.2 (59)	2.9 ±1.6 (19)	0.6 ±0.3 (37)	162* ± 94 (37)	29** ±28 (37)	11.2 ±12.0 (44)
Low villages in endemic area	6.5±1.3 (58)	3.1 ±0.9 (16)	0.7 ±0.4 (26)	124 ± 74 (26)	42 ±37 (26)	16.2 ±15.1 (25)
Goitrous in endemic area	7.2±0.8 (84)	2.3 ±2.2 (16)	0.5* ±0.3 (21)	153 ±116 (21)	30 ±34 (21)	6.7** ± 7.1 (22)
Non-goitrous in endemic area	6.7±1.3 (117)	3.0 ±1.3 (35)	0.7 ±0.3 (63)	137 ±106 (63)	35 ±32 (63)	13 ±13.3 (69)
Australian normal range	5.5—8.3	10—15	0.8—1.8	80—180	80—180	70—140

* $P<0.05$
** $P<0.01$
*** $P<0.001$

using t-test for comparison of various groups. The figures given are for the mean ± the standard deviation, with the number of subjects tested shown in parentheses.

Total urinary nitrogen. This was found to be low throughout the population of the endemic area and there was no significant difference between high and low villages (Table 2). However, the mean for the population of the area (2.7 g/24 h ± 1.7g/24 h) was significantly lower than that found in coastal villagers (mean 6.8 g/24 h ± 5.5 g/24 h).

These values were below the accepted normal for Adelaide of 10 g/24 h to 15 g/24 h.

Urinary creatinine. There was a significant difference between goitrous (mean 0.5 g/24 h ± 0.3 g/24 h) and non-goitrous persons (mean 0.7 g/24 h ± 0.3 g/24 h). (Table 2.) There was, however, no significant difference observed between high and low villages.

All these values and the mean for the population of this area were below the normal Adelaide minimum of 0.8 g/24 h. The mean level in the coastal villages (1.1 g/24 h ± 0.52 g/24 h) was within the normal range, and significantly higher ($P < 0.001$) than the mean for the whole endemic area population.

Urinary sodium. Although the urinary sodium in healthy persons may vary according to diet, the levels of urinary sodium in New Guinea subjects were found to be consistently low. Table 2 shows the mean level in the high villages (29 mEq/24 h ± 28 mEq/24 h) to be significantly lower than that in the low villages (42 mEq/24 h ± 37 mEq/24 h). The whole endemic area population examined was found to have a mean of 32 mEq/24 h ± 35 mEq/24 h, which was significantly lower than the figure for the coastal villagers (77 mEq/24 h ± 56 mEq/24 h), a result below normal for a European population.

Urinary potassium. Urinary potassium was significantly higher ($P < 0.05$) in the high villages (mean 162 mEq/24 h ± 94 mEq/24 h) than the low villages (mean 124 mEq/24 h ± 74 mEq/24 h). Similarly the value for the goitrous area (mean 149 mEq/24h ± 80 mEq/24 h) was significantly higher than that for the coastal group in Lae (mean 41 mEq/24 h ± 39 mEq/24 h).

Discussion

People of the Wain and Naba (like many others of New Guinea) live largely on sweet potato and other root vegetables, such as taro. Some fruit and vegetables are eaten occasionally, as described earlier in this paper.

Bailey (1963a) found that the protein content of sweet potatoes was 1.1% while taro and yam contained 2.4% and 2.5% protein respectively. The calorific value of sweet potato was approximately 100 calories per 100 g.

Usually these people eat one main meal a day, generally in the evening. It is obvious from the above figures that large quantities of food must be consumed to give the calories and protein necessary to sustain life.

If the total urinary nitrogen per day is expressed as dietary protein in grams per day the population of the endemic area have an average daily protein intake of 2.1 × 6.5, which is approximately 18 g/24 h (Harper, 1963). The recommended daily protein intake for the United States of America is 1 g per kg of body-weight, so that in the Huon peninsula people the figure should be approximately 60 g/24 h.

The figures given by Choufoer et al. (1963) showed a deficiency of protein in the Mulia area, where the daily protein intake was estimated at between 10 g/24 h and 20 g/24 h.

Further evidence of protein deficiency comes from the urinary creatinine values, which were well below normal. Regular checking with the volunteers by New Guinean orderlies in the field team verified the completeness of the urine samples. To be absolutely sure of complete 24-hour samples, any specimens below 300 ml were discarded. It appears that, even though some specimens of urine were below 400 ml, reliable 24-hour specimens were obtained.

Creatinine is derived from three amino-acids—glycine, arginine and methionine (Harper, 1963). Methionine is an essential amino-acid. Luyken & Luyken-Koning (1962) state that sweet potato is relatively rich in nitrogen (7.66 ± 1.64 mg/100 g potato) but low in sulfur-containing amino-acids. Methionine, a source of urinary creatinine, is a sulfur-containing amino-acid. Thus our urinary creatinine findings are consistent with the views of these workers. The fact that the urinary creatinine values rose as altitude decreased, indicated (as do the urinary nitrogen studies) that people living at the higher levels are less well-nourished than the rest of the population.

Despite the lack of protein in the diet, and despite the lack of animal protein, cases of kwashiorkor were not seen in this survey, but a few cases of infant malnutrition were found. Breast-feeding for up to 2 or more years is common, and the richness of breast milk in protein (Bailey, 1963a, 1963b) together with a high infant mortality in weaker children probably explains the apparent health of these children. Serum protein levels were found to be

normal (Table 2). Choufoer et al. (1963) showed that at Mulia and Tiom, in West Irian, the total serum proteins were normal and the albumin fraction often low with the globulin always high. The findings in the Wain and Naba area were consistent with this, although only a few analyses of total albumin and globulin were performed.

The urinary electrolytes indicated increased potassium levels, with a very much reduced sodium level, even in the diet of coastal people, who eat some meat and imported rice. Much of the food for the coastal group in Lae comes from inland, although it is largely produced in the Markham River valley. Thus the indications were of a very low salt diet, with salt deficiency being significantly greater in the people living higher up the mountains. The inhabitants of the endemic area are now obtaining some salt from Lae and from the mission station, so that their original sodium intake, 20 years ago, was probably even lower than at present.

These nutrition indices raised the question of normality. The figures for creatinine, total nitrogen and sodium were very much lower than those recommended for European diets. It is difficult to compare European and Pacific peoples, but Bailey (1963b) states that malnutrition in New Guinea is manifested by reduced height, weight, and quantities of subcutaneous fat. Even the coastal group at Lae, having characteristics considered normal in New Guineans, were eating a diet which is below normal European nutrition standards.

Most likely these people are truly malnourished, particularly as there has been in the past, and still is today, a very rigorous selection of the fittest, as discussed earlier. Thus, the population has become adapted to multiple nutritional deficiencies, including iodine deficiency, although they will obviously benefit greatly from the improved diet planned for the future.

STUDIES OF THE EFFECT OF IODIZED OIL

To investigate the effect of iodized oil, 4 ml of iodized essence of poppy-seed oil (Neo-Hydriol, in fluid form) were given by deep intramuscular injection. In the initial campaign of McCullagh in 1957, some 10 252 persons were examined and goitrous persons and those over 50 years of age were excluded from the trial. Of the remaining population (totalling 7881), half (3934) received an injection of Neo-Hydriol while the others (3947) were given a control injection of saline.

During his survey in 1962, Hennessy reinjected those persons previously injected with Neo-Hydriol in the 28 villages of the Wain, while previously injected persons in the Naba were injected some 8 months before our first visit by a medical assistant.

Upon arrival of the present field party in the Wain in 1964, 61 persons with size-2 or size-3 goitres were injected also, and they were examined some 3 months later. Further observations have since been made in 1966. There were therefore six groups in this study: (*a*) untreated or saline-treated; (*b*) treated 4½ years before; (*c*) treated 3 years before (Wain villages only); (*d*) treated 18 months before (Naba villages only); (*e*) treated 3 months before; and (*f*) coastal New Guineans from the Lae Hospital.

Results

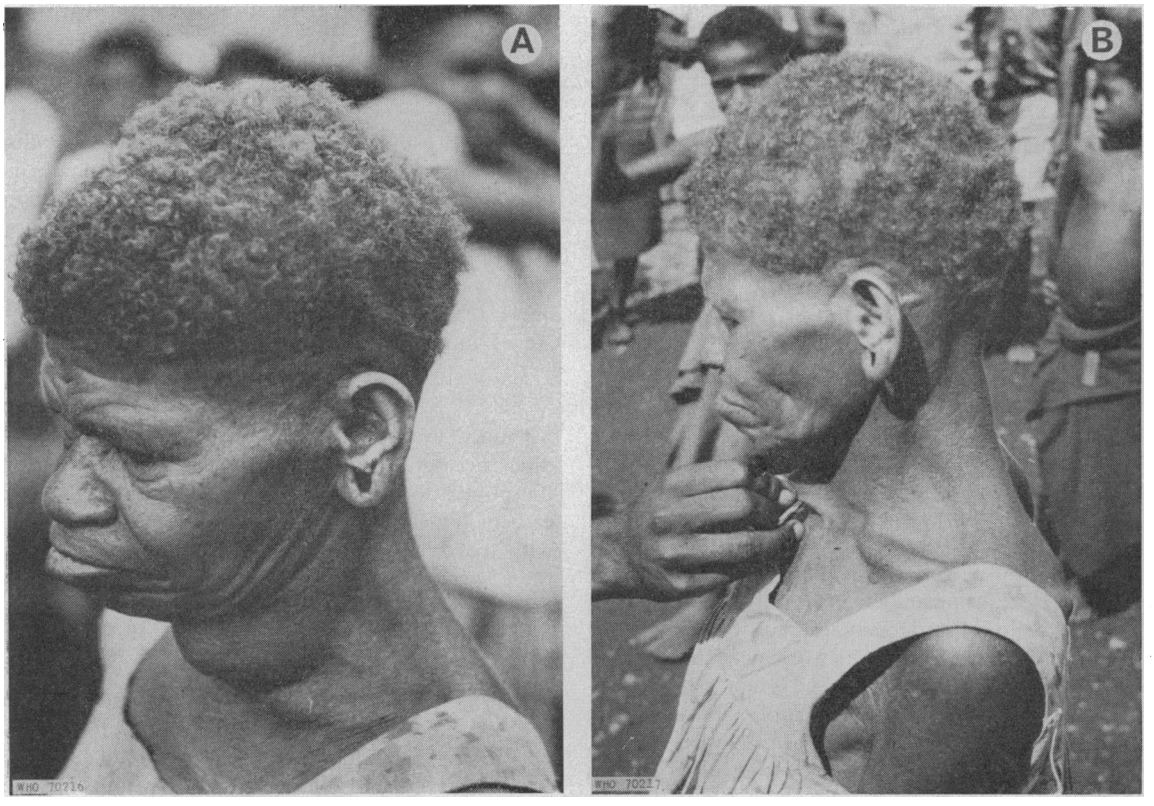
Clinical examination did not reveal any significant difference between treated and untreated members of the population. In particular, it was noted that no case of hyperthyroidism was found. Some persons with parotid gland enlargement were seen, but these were common in both groups and in other areas of New Guinea where iodine prophylaxis has not yet begun.

Clinical effects. Of the 61 persons with easily visible goitres who were injected 3 months before the second examination, 60 of them had goitres which became reduced in size enough to convince both observers and the villagers themselves that the reduction was significant. In 27 of these 60 cases there had been a change in goitre size from size 2 to size 1, and 5 others changed from size 2 to size 0. A representative goitrous New Guinean before and after treatment is shown in Fig. 10.

Urinary iodine. Results for the 24-hour urinary iodine values are given in Table 3 and compared with normal subjects in Adelaide. The mean value for New Guineans injected 3 years before (35 μg/24 h) was lower than that for those treated 18 months before (119 μg/24 h) but higher than that for those treated 4½ years before (23 μg/24 h). This latter group still showed an elevated urine iodine level above that of the untreated subjects. Some of the data are shown graphically (Fig. 11).

^{131}I *uptake.* The uptake at 24 hours was significantly lower in subjects treated 18 months before (mean 31%), 3 years before (mean 37%) and 4½ years before (mean 44%) than in untreated controls (Table 3). In those treated 3 months before the values obtained were below normal limits for

FIG. 10
NODULAR GOITRE IN A NEW GUINEAN (A) BEFORE AND (B) 3 MONTHS AFTER INJECTION OF IODIZED OIL



untreated persons in Adelaide, the mean being 6.0%. There was no significant difference between those treated 3 years before and those treated 18 months before.

Serum PBI. The results of the serum PBI estimations can be seen in Table 3 and in Fig. 12. The combined mean value for persons treated 3 years and 18 months before was 8.0 μg/100 ml, and for those treated 4½ years before it was 6.4 μg/100 ml. All these figures were significantly greater than those for the untreated endemic area groups. In persons treated 3 months before the mean serum PBI was 44.7 μg/100 ml.

Serum butanol-extractable iodine. BEI determinations in 7 treated cases had a mean of 5.9 μg/100 ml ± 1.1 μg/100 ml, which was at the upper limit of the normal range (3-6 μg/100 ml). This indicates that the hormonal iodine in the serum was within normal limits.

T_3 resin uptake. Determinations of the T_3 resin uptake (Table 3) revealed a significant difference between the treated and untreated. It was noted that while, in all treated groups, the serum PBI was above the normal range for the Australian population in Adelaide, the value for the T_3-resin uptake was within normal limits, except in those treated 3 months before (mean 110%).

Discussion

The goitres were multinodular, particularly in older persons. Histological section revealed that they were hyperplastic with little or no colloid (Fig. 13). Their striking regression following iodized oil indicates that correction of iodine deficiency in persons with hyperplastic, iodine-deficient goitre causes a return to normal, although a small residual goitre may remain. Unfortunately,

TABLE 3

THE EFFECT OF IODIZED OIL ON THYROID FUNCTION IN NEW GUINEA SUBJECTS [a]

Group	Urinary iodine (μg/24 h)	^{131}I uptake (% at 24 h)	Serum PBI (μg/100 ml)	T_3 resin uptake (% of normal)
Untreated	11.5± 12.4 (91)	70±19 (181)	4.1± 2.1 (204)	91±12.1 (195)
Treated 18 months and 3 years before	67 ± 83 (47)	33±20 (94)	8.0± 2.0 (79)	97±14.8 (77)
Treated 3 months before	258 ±109 (8)	6.0 ± 3 (20)	44.7±18.4 (20)	110±15.5 (20)
Treated 18 months before	119 ±114 (18)	31±20 (51)	8.2± 2.6 (27)	97±15.8 (27)
Treated 3 years before	35 ± 25 (29)	37±19 (43)	7.8± 1.6 (52)	97±14.7 (50)
Treated 4 ½ years before	23 ± 21 (11)	44±18 (67)	6.4 ± 2.4 (43)	99± 16.0 (43)
Australian normal range	70—140	16—40	3.6—7.2	70—110

[a] Statistical analysis showed highly significant differences between the treated and untreated groups in urinary iodine, ^{131}I uptake and serum PBI ($P<0.001$). There was no significant difference in the ^{131}I uptake or serum PBI between subjects treated 3 years and 18 months before. The figures given are for the mean ± the standard deviation, with the number of subjects tested shown in parentheses.

no glands in persons treated by this method have been available for histological section.

Marine & Lenhart (1909) showed that iodine-deficient glands in dogs would give rise to colloid goitre if iodine was replaced in physiological doses. However, they found that larger doses caused a return of the enlarged gland to normal. This was confirmed by Marine & Kimball (1920) in other experimental animals.

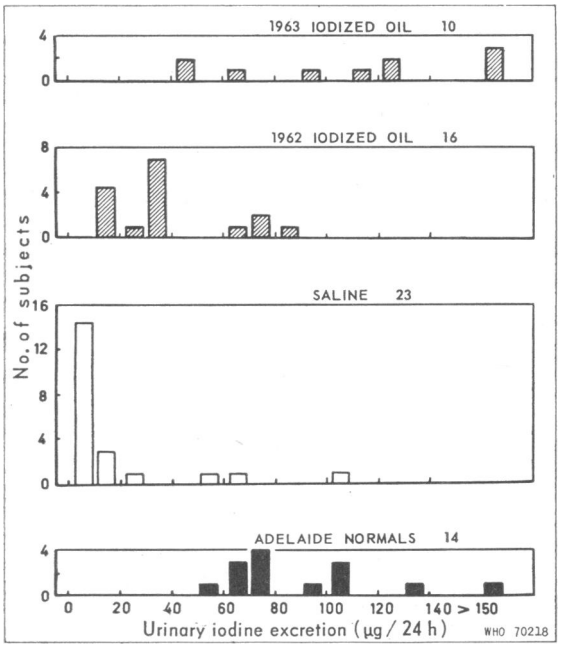
The striking regression of goitre in New Guineans treated with oil indicates that pituitary secretion of TSH was diminished owing to production of normal quantities of thyroid secretion following correction of iodine deficiency. The results of serum TSH estimations supported this view in that no detectable activity could be demonstrated in goitrous persons who had been treated 3 months before in contrast to untreated goitrous subjects in whom an excess could be shown (Buttfield et al., 1966). The normal BEI values in the treated persons also indicate that normal quantities of hormone were present in the serum. Finally the raised T_3-resin uptake in the treated subjects also suggests an increase in hormonal iodine.

The laboratory data indicate an excess of iodine present in the serum detectable for at least 4½ years. The elevated PBI values were most likely due to iodine-containing lipids being bound to plasma protein. It can be assumed from the data that PBI and T_3-resin uptakes rose above normal levels at 3 months owing to iodine absorption, while the ^{131}I-uptake figures fell below normal for the same reason.

The main difference between the treated groups was in the urinary iodine estimations. Those treated 18 months before had a 24-hour excretion of iodine in the normal range. Those treated 4½ years and 3 years before had a value for urinary iodine

FIG. 11

URINARY IODINE DETERMINATIONS CARRIED OUT IN 1964 ON NEW GUINEANS GIVEN IODIZED OIL 18 MONTHS BEFORE (1963) AND 3 YEARS BEFORE (1962) COMPARED WITH THOSE IN UNTREATED NEW GUINEANS AND AUSTRALIANS IN ADELAIDE



which was below the limits usually accepted as normal, but this figure was still above the mean value for untreated New Guineans in the endemic area though less than the value for coastal villagers. However the ^{131}I-uptake was at the upper limit of the normal range after 4½ years and the plasma PBI was still elevated. Hence it is evident that the store of iodine in the blood was still present 4½ years after injection, and the thyroid gland did not show the grossly elevated radioiodine uptake demonstrable in untreated New Guineans.

Carter et al. (1959) and Clarke et al. (1960) were able to show that, following administration of iodized oily radiopaque media (Lipidol and Neo-Hydriol respectively), the PBI rose and then fell rapidly to near the normal range in 3-4 months. The ^{131}I-uptake fell to below normal and slowly rose over a period of up to 18 months while the PBI continued its slow fall towards normal during the same period, but both parameters were still abnormal at the conclusion of these authors' experiments. These findings of previous workers, of a rapid rise and initially rapid fall of PBI, have been confirmed by the PBI values found in the Huon peninsula. If the iodine was not in the form of a chemical compound, as in the case of Neo-Hydriol, but merely iodine absorbed on to oil, then the free iodine would probably have been excreted within a few days. However, Neo-Hydriol (made by treating esters of poppyseed oil with hydriodic acid) is probably bound on the plasma protein as a lipo-protein complex which acts as a store for slow release.

Stanbury et al. (1954) in Mendoza, Argentina, showed that the quantity of iodine retained by goitrous glands in an endemic goitre area was related to the daily dose of iodine administered. One patient, taking 1500 µg/day, developed thyrotoxicosis (Stanbury et al., 1954). These authors found that the time taken for iodine-deficient glands to return to normal function, when presented with iodine replacement, was approximately 100-120 days. With the depot iodine replacement therapy used in the Wain and Naba in New Guinea, it was clear that there would be a high dose of iodine available to the gland within a few days of injection. However, no person with thyrotoxicosis has been seen in this area.

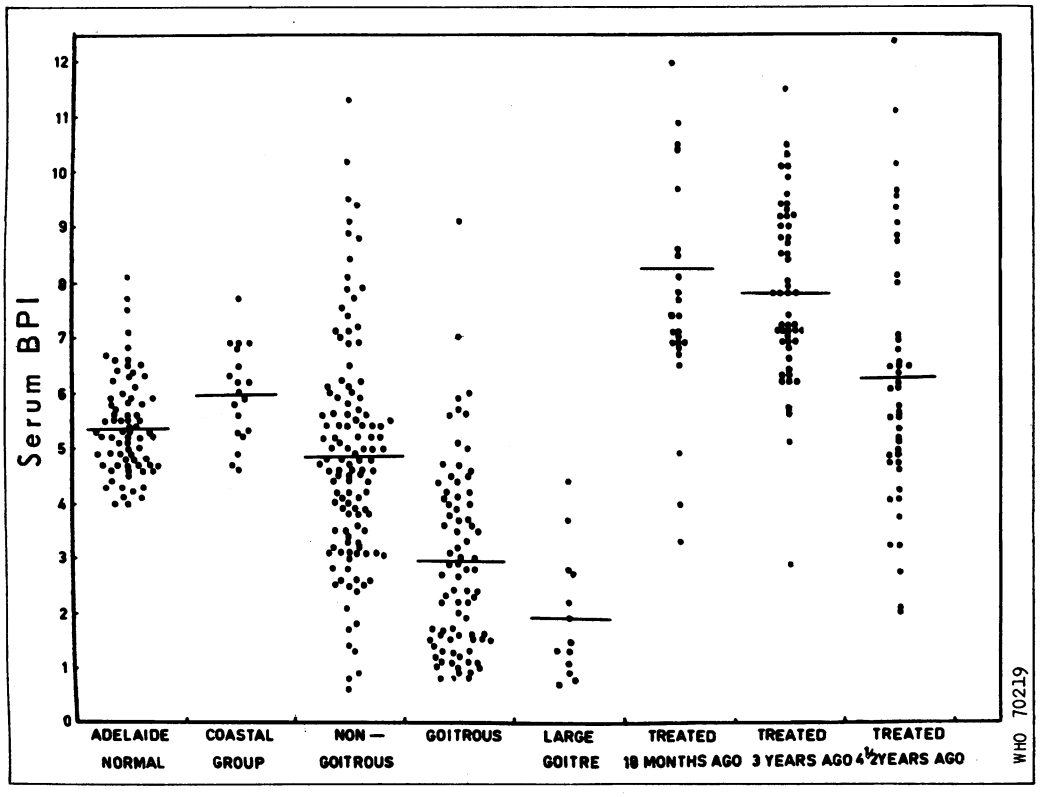
As reported elsewhere (Buttfield et al., 1966) serum TSH was biologically normal with the McKenzie assay, i.e., the maximum increase of ^{131}I in the blood was at 3 hours, which means that no long-acting thyroid stimulator (LATS) was detected (Hoffmann & Hetzel, 1966). At 3 months, the mean urinary iodine excretion was still greater than 250 µg in 24 hours, so that it is probable that the excess iodine presented to the thyroid gland inhibited the uptake of ^{131}I and release of thyroid hormone (Wolff & Chaikoff, 1948; Braverman & Ingbar, 1963). Because of the continuous exposure of the gland to iodine it is possibly less likely that iodine-deficient glands being repleted with iodized oil will become overactive, giving rise to thyrotoxicosis. However, if LATS or an autonomous nodule were present, it is possible that thyrotoxicosis might develop.

It is also of interest that none of the other possible complications was seen. No case of foreign body reaction to Neo-Hydriol was found and no case of either acute or chronic iodism was seen.

The findings indicate that iodine deficiency was substantially corrected for over 4 years after oil administration. This finding fits with the significant benefit reported by Hennessy (1964) in the prevention of goitre for as long as 5 years after the original oil administration by McCullagh.

FIG. 12

SERUM PBI IN TREATED AND UNTREATED GROUPS IN NEW GUINEA AND AUSTRALIA



Calculation of the loss of iodine in the urine from estimations carried out at various intervals after the injection of iodized oil indicates that sufficient iodine may remain after a dose of 4 ml (2.15 g iodine) to cover an iodine requirement of 100 μg/day for up to 5 years.

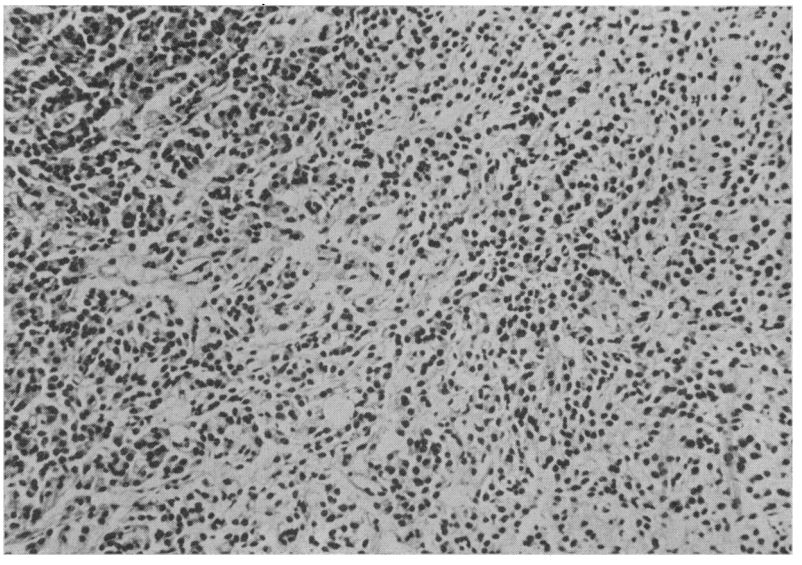
The iodized oil has been found suitable for mass injection campaigns. Correction of iodine deficiency is of particular importance in children and in women of child-bearing age. Iodized oil injection is therefore recommended for certain correction of iodine deficiency in these two groups of an iodine-deficient population whenever there is uncertainty as to the efficacy of other measures.

Follow-up studies are now being initiated to determine the effect of iodized oil administration on the neurological defects, such as mental deficiency and deaf mutism, previously reported in New Guinea (Choufoer et al., 1965; McCullagh, 1963b; Hennessy, 1964).

Iodine prophylaxis of endemic goitre has been attempted in many ways since the pioneer studies of 150 years ago. However, it has been generally accepted in more recent years that " iodization of salt is the most practical method of administering iodine to a population " (WHO Study Group on Endemic Goitre, 1953). In New Guinea, and probably in other underdeveloped or primitive areas, there are many reasons why iodized salt is not particularly suitable. Firstly, communication in mountainous areas is difficult so that salt, a heavy commodity, has to be carried by light aircraft and then on foot for long distances. Secondly, because of the severity of iodine deficiency, salt would have to be more heavily iodized than usual, or larger quantities of salt would need to be eaten. Both these possibilities involve considerable expense. There is also the objection that supplies of iodized salt in such terrain will necessarily be very irregular. Iodized salt might become a valuable commodity which would be traded with neighbouring groups.

FIG. 13

HISTOLOGICAL SECTION OF LARGE GOITRE REMOVED BECAUSE OF PRESSURE SYMPTOMS, SHOWING INTENSE HYPERPLASIA WITH NO COLLOID



Iodized oil offers a cheap[1] alternative to iodized salt and has the advantage that administration every 4-5 years provides a certain and virtually complete correction of iodine deficiency. Regular injection by relatively unskilled medical orderlies is practicable; and once the oil has been administered, certain correction of the deficiency has been achieved, which is difficult to ensure with iodized salt. The striking regression of goitres makes for good publicity for the health team and government authorities, and therefore helps to ensure a successful public health campaign.

[1] US $4.92 per 100-ml vial (25 adult doses).

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RÉSUMÉ

Le goitre endémique existe depuis de nombreuses années en Nouvelle-Guinée orientale et sa fréquence est particulièrement élevée dans la péninsule de Huon. Les conditions locales rendant difficile la prophylaxie par le sel iodé, on a eu recours depuis 1957 à l'administration intramusculaire d'une suspension d'iode dans l'huile d'œillette (4 ml=2,15 g d'iode). Des enquêtes menées en 1960 et 1962 ont montré une diminution de l'incidence de l'affection chez les sujets traités, et de nouvelles séries d'injections ont été pratiquées en 1962 et 1963.

En 1964, les auteurs ont conduit une étude du métabolisme iodé parmi les habitants de la région. Les recherches ont porté surtout sur les valeurs d'iodocaptation, déterminées par scintillométrie (10-30 habitants de chacun de 16 villages), et d'excrétion de l'iode dans l'urine de 24 heures (200 personnes examinées).

On a constaté une carence iodée grave (iodurie: 11,5 μg/jour; fixation d'^{131}I: 70%) chez les sujets non traités, ainsi qu'une carence protéique, une diminution du taux de sodium urinaire et une élimination accrue de potassium. Chez les sujets traités en 1957, l'excrétion urinaire de l'iode et l'iodocaptation étaient similaires à celles observées chez les témoins non traités. Trois ans après l'administration d'huile iodée, l'iodurie était notablement plus élevée (35 μg/jour); elle atteignait 23 μg/jour 4½ après le traitement. Le taux de fixation de l'iode était abaissé (37% après 3 ans et 44% après 4½ ans). Chez les sujets traités, le taux d'iode sanguin combiné aux protéines était encore élevé 4½ ans après l'administration d'huile iodée. Trois mois après l'administration du traitement prophylactique, on notait des valeurs de fixation de l'iode radioactif de l'ordre de 6% et chez 60 sur 61 des sujets traités, le goitre avait fortement régressé.

Ces résultats confirment le rôle de la carence iodée dans l'apparition du goitre. Cette carence peut être efficacement combattue par l'administration à dose unique d'huile iodée qui assure les besoins de l'organisme en iode (100 μg/jour) pendant 5 ans environ. Cette méthode commode et peu coûteuse convient parfaitement à la prophylaxie de masse. Aucun effet secondaire (thyréotoxicose, iodisme) n'a été observé à la suite de l'application du traitement à plus de 2000 personnes. De nouvelles recherches sont actuellement entreprises pour évaluer l'efficacité de la méthode pour la prévention des cas d'arriération mentale et de surdi-mutité.

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