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**Research Article**

Previous studies of thyroid function during various infections have yielded conflicting results, but most have suggested an acceleration of peripheral thyroxine ($T_4$) turnover during the acute infectious illness. In the present studies, thyroid function was examined by a method allowing simultaneous analysis of both endogenous thyroidal release and peripheral $T_4$ disposal in normal volunteers after induction of acute falciparum malaria. Subjects received iodide$^{125}$I, followed in 5-7 days by $^{131}$I-$T_4$ intravenously. 4 days later, infection was induced by the injection of parasitized red blood cells. Bidaily measurements of serum protein-bound $^{125}$I and protein-bound $^{131}$I, and urinary $^{125}$I and $^{131}$I, together with frequent estimates of serum $^{127}$I-$T_4$ (Murphy-Pattee) and free $T_4$ ($FT_4$), were made during a control period, during acute illness, and during convalescence. Alterations in the peripheral metabolism of $^{131}$I-$T_4$ during infection included significant decreases in the fractional disappearance rate for $T_4$ [(k)], and in the clearance and daily disposal of $T_4$, all of which returned to control values during convalescence. Total serum $^{127}$I-$T_4$ increased late in the infected period to become greater during convalescence than either before or during infection, while $FT_4$ did not increase significantly until convalescence. An analysis of serum $^{131}$I-$T_4$/$^{127}$I-$T_4$ and $^{131}$I-$T_4$/PB$^{125}$I ratios confirmed these observations. The slope with time of ratios for urinary $^{125}$I/$^{131}$I, a reflection of thyroidal iodine release, was decreased during infection, but rebounded […]



# Alterations in Thyroid Iodine Release and the Peripheral Metabolism of Thyroxine during Acute Falciparum Malaria in Man

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ABSTRACT Previous studies of thyroid function during various infections have yielded conflicting results, but most have suggested an acceleration of peripheral thyroxine ($T_4$) turnover during the acute infectious illness. In the present studies, thyroid function was examined by a method allowing simultaneous analysis of both endogenous thyroidal release and peripheral $T_4$ disposal in normal volunteers after induction of acute falciparum malaria. Subjects received iodide-$^{125}I$, followed in 5–7 days by $^{131}I$-$T_4$ intravenously. 4 days later, infection was induced by the injection of parasitized red blood cells. Bidaily measurements of serum protein-bound $^{125}I$ and protein-bound $^{131}I$, and urinary $^{125}I$ and $^{131}I$, together with frequent estimates of serum $^{127}I$-$T_4$ (Murphy-Pattee) and free $T_4$ ($FT_4$), were made during a control period, during acute illness, and during convalescence. Alterations in the peripheral metabolism of $^{131}I$-$T_4$ during infection included significant decreases in the fractional disappearance rate for $T_4$ [(k)], and in the clearance and daily disposal of $T_4$, all of which returned to control values during convalescence. Total serum $^{127}I$-$T_4$ increased late in the infected period to become greater during convalescence than either before or during infection, while $FT_4$ did not increase significantly until convalescence. An analysis of serum $^{131}I$-$T_4$/$^{127}I$-$T_4$ and $^{131}I$-$T_4$/PB$^{125}I$ ratios confirmed these observations. The slope with time of ratios for urinary $^{125}I$/$^{131}I$, a reflection of thyroidal iodine release, was decreased during infection, but rebounded to control values during the convalescent period. The observed increments in serum $^{127}I$-$T_4$ concentration in the convalescent phase may reflect in part the slowing of (k), but together with the rising ratios of urine $^{125}I$/$^{131}I$ suggests enhanced thyroidal $T_4$ secretion immediately after the acute illness. Thus, with malarial infection, there appears to be an initial depression followed by a rebound in rates of thyroidal iodine release. In contradistinction to other infections, fractional turnover and daily disposal of hormone is decreased in malaria, perhaps due to hepatic dysfunction and the consequent impairment in cellular deiodinative processes.

## INTRODUCTION

The great majority of studies of thyroid function during naturally acquired or experimentally induced infections in man and animals have suggested that the fractional rate of peripheral turnover [(k)][1] of thyroxine ($T_4$) is accelerated under such conditions (1–5). Those studies which have attempted to assess the rate of thyroidal iodine release during acute illness, either by direct serial epithyroid count rates after $^{131}I$ administration, or by changes in the concentration of stable $T_4$ in serum. have indicated that initially there often occurs an inhibition of release which may then be followed by a rebound hypersecretion during recovery (6–9).

During the course of studies of various metabolic responses to experimentally induced falciparum malaria in man, we observed that (k) was slowed rather than accelerated during this illness. Consequently, a study was

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[1] *Abbreviations used in this paper:* $AFT_4$, concentration of free thyroxine; $FT_4$, free thyroxine; I*, inorganic radioiodine; (k), fractional rate of thyroxine turnover; PB, protein-bound; $PFT_4$, per cent of free thyroxine; RAIU, fractional uptake of $^{131}I$; SGOT, serum glutamic oxaloacetic acid transaminase; SGPT, serum glutamic pyruvic transaminase; $T_3$, triiodothyronine; $T_4$, thyroxine; TDS, thyroxine distribution space; TSH, thyrotrophin; U, urinary.

done to define more clearly the nature of the thyroidal response to acute malaria. Malarial infection appears to be a convenient experimental model, since it is possible to control the onset of acute illness within certain limits, and the infection is readily cured with appropriate therapy. A recently described double isotope technique was utilized which allows simultaneous assessment of both endogenous thyroidal iodine secretion rates as well as the usual indices of peripheral $T_4$ turnover (10). In the assessment of thyroidal iodine release, the method offers several advantages over the serial epithyroid counting technique, in view of interpretive and technical shortcomings inherent in the latter method. Another very similar method for estimating thyroidal iodine release (11) was also employed. To our knowledge, this is the first time these methods have been used in man to examine the sequential changes in thyroid hormone metabolism that occur during infection.

## METHODS

Studies were performed in 12 euthyroid male volunteer prisoners with no history of either thyroid disease, prior malarial infection, or recent infectious illness. A thorough explanation of the character and risks of experimental malarial infection was presented both orally and in writing to each volunteer. Studies were conducted on the Malaria Research Unit of the Harry S. Truman Laboratory of Comparative Medicine, located in the Jackson County Jail at Kansas City, Mo. In those subjects who developed acute malarial infection, each study consisted of five periods: a control period, a prodromal period, early and late acute illness periods, and a period denoted as "convalescence." The interval designated "prodrome," was that period between the injection of parasites and the onset of infection. The period of clinical infection was defined by the presence of fever and parasitemia and was divided into early and late portions of similar duration. Data were analyzed throughout the prodromal, and the early and late phases of induced infection to assess the possibility of either very early, or transient changes in $T_4$ metabolism that might otherwise have been overlooked. The convalescent period was comprised of observations after therapy and decrudescence of illness when evidence of infection was gone. The duration of each study period ranged from 3 to 6 days and the total duration of each complete study varied from 23 to 30 days.

The general experimental protocol was as follows: Each of eight subjects was given 150 $\mu$Ci of $^{125}I$ i.v. in order to label the intrathyroidal iodine pool. Thereafter, bloods were drawn at 12-hourly intervals and all urine was collected on a 12-hourly basis. Samples of serum were incubated with an anion exchange resin to remove free $^{125}I$, after which the concentration of protein-bound $^{125}I$ in serum ($PB^{125}I$) and total urinary $^{125}I$ were measured. When the concentration of $PB^{125}I$ had reached an approximate plateau (usually at 7–10 days), 50 $\mu$Ci of $^{131}I$-labeled $T_4$[2] was administered i.v. in a single dose, in order to label the peripheral hormonal ($T_4$) pool. Thereafter, both $PB^{125}I$ and $PB^{131}I$ in serum, as well as urinary $^{125}I$ and $^{131}I$ were measured in a dual-channel well-type scintillation counter, corrections being made for the contribution of counts from $^{131}I$ into the counting range of $^{125}I$. Values for each isotope in serum were calculated and expressed as a per cent of the original administered dose per liter, and in urine as a per cent of the administered dose per 12-hr collection.

After a control period of usually 4 days duration, subjects were infected with the Uganda I strain of *Plasmodium falciparum* by intravenous injection of $2 \times 10^7$ parasitized red blood cells taken from a blood-citrate-glycerin preparation that had been frozen in liquid nitrogen. Symptoms of malaise, fatigue, and headache without fever or parasitemia, were characteristic of the prodromal period. Antimalarial therapy was begun after 1 day of fever and after 2 or more days of parasitemia. All but two of the patients who developed acute illness were treated with 6,8-dichloro-2-(3',4'-dichlorophenyl)-$\alpha$-(di-*n*-butylaminomethyl)-4-quinoline methanol-HCl (WR-30090) in a dosage of 230 mg every 8 hr for nine doses. The remaining two subjects (E. B. and D. G.) were treated with 6-bromo-$\alpha$-(diheptylaminomethyl)-9-phenanthrene-methanol-HCl (WR 33063) in a dosage of 200 mg every 6 hr for 24 doses. In order to examine the possible effects of the antimalarial drug WR 30090 itself on the parameters of $T_4$ metabolism examined, two additional volunteers were studied exactly as above except that a placebo injection of their own blood was given instead of malarial parasites.

In six patients, studies were carried out precisely as described above. In two additional patients the protocol varied only in that methimazole (30 mg every 6 hr) was begun 1 day before administration of the $^{131}I$-labeled $T_4$ and was continued throughout the period of study. Methimazole blockade was utilized to prevent recycling of radioiodine liberated peripherally from the $^{131}I$-$T_4$, to gain confirmation of observations obtained in the patients studied in the absence of blockade.

In two other subjects, the initial isotope injected was $^{125}I$-$T_4$ (75 $\mu$Ci) followed in 5 days by injection of malarial parasites. At the onset of acute illness, which developed in only one of these subjects, an injection of 50 $\mu$Ci $^{131}I$-$T_4$ was given i.v. This was done to demonstrate that observed changes in turnover were due to infection and were not a function of time or recycling of radioiodine. Data from the subject who did not develop clinical malaria are included since they provide control observations for the changes with time in values for $PB^{125}I$ and urinary $^{125}I$ after injection of parasites, but in the absence of development of acute illness. Both of these patients received methimazole throughout the study.

Estimations of the dialyzable fraction ($PFT_4$) of thyroxine by an equilibrium dialysis technique (12), and of the concentration of stable $T_4$ ($^{127}I$-$T_4$) in serum by the method of Murphy, Pattee, and Gold (13) were obtained on multiple samples during each of the three major experimental periods and are expressed throughout as $T_4$-iodine.[3]

From the foregoing data a number of calculations were made. The kinetics of the peripheral metabolism of $^{131}I$-$T_4$ were assessed by methods described in detail elsewhere (14). The fractional rate of peripheral turnover of $T_4$ was cal-

[2] $^{131}I$-labeled $T_4$ was obtained from Abbott Laboratories, North Chicago, Ill. Sterile carrier-free $^{125}I$ was obtained from the Iso-Serve Division of Cambridge Nuclear Corp., Cambridge, Mass.

[3] Performed by the Boston Medical Laboratory, Waltham, Mass., with a number of duplicate total $T_4$ analyses by the same method performed by Mrs. Loretta Argrett of the Walter Reed Army Institute of Research.

culated from the semilogarithmic regression slope of serum $PB^{131}I$, as determined by the method of least squares. Data obtained during the initial 36–48 hr after injection were omitted from these calculations to allow equilibration of the $^{131}I$-$T_4$. $T_4$ distribution space (TDS) was calculated from the zero time intercept of the least squares regression equation as the quotient of the injected radioactivity and the concentration of radioactivity in serum at the time of injection. Estimation of TDS during infected and convalescent periods were modified however. The percentage of the injected $^{131}I$-$T_4$ remaining in the body at the beginning of these two experimental periods was calculated from the fractional turnover rate during the immediately preceding period. The TDS was then calculated as the quotient of this estimate of $^{131}I$-$T_4$ remaining and the simultaneous $PB^{131}I$ concentration obtained from the calculated regression equation for the period examined (15). Peripheral $T_4$ clearance rate was calculated as the product of TDS and the fractional turnover rate. The daily $T_4$ disposal rate was calculated as the product of the $T_4$ clearance rate and the serum $^{127}I$-$T_4$ concentration (16).

The ratio $PB^{131}I$: $PB^{125}I$ was calculated for each specimen of serum obtained. In addition, the ratio $PB^{131}I$: $^{127}I$-$T_4$ was calculated for each of the frequently obtained specimens in which $^{127}I$-$T_4$ had been determined. The changes with time in the ratio $PB^{131}I$: $^{127}I$-$T_4$, and other data directly referable to stable $T_4$ measurements (Table I) were examined during three (control, infected, convalescent) rather than five periods since a limited number of sera were analyzed for $^{127}I$-$T_4$. For each study period, the slopes and standard errors of the curves described by these ratios were calculated as a semilogarithmic function of time by the method of least squares.

Calculations based upon urinary radioiodine included ratios of urine $^{125}I$: $^{131}I$ and $U^{125}I$: $PB^{125}I$ and $U^{131}I$: $PB^{131}I$ throughout the various periods of study. Urine specimens began and ended at the time of blood collection. Values for protein-bound radioiodine used in calculating the foregoing ratios were the logarithmic mean of those in the initial and terminal serum samples for each period. The values for $U^{131}I$: $PB^{131}I$ constitute a "partial" deiodinative clearance rate, representing that portion of total deiodinative clearance that is reflected in urinary radioiodine excretion (17, 18). The values for the ratio of $U^{125}I$: $PB^{125}I$ in addition reflect nonthyroxine iodine release from the thyroid (19).

## RESULTS

*Turnover of $^{131}I$-$T_4$ (Table I).* The values for various aspects of the peripheral turnover of exogenously labeled $T_4$ are shown in Table I, and are expressed throughout as $T_4$-iodine. The values obtained in both the control and convalescent periods are characteristic of those generally found in euthyroid patients (14, 16). Eight patients, studied with the double isotope method described above, developed acute malarial infection. During the control period, the thyroxine distribution space (TDS) averaged 8.79±1.68 liters (mean±SD), the fractional rate of $T_4$ turnover [(k)] averaged 12.1± 2.2%/day, and the $T_4$ clearance rate was 1.05±0.19 liters. Also within the normal range for adults were values for $^{127}I$-$T_4$ concentration (4.2±0.5 μg/100 ml) and for total daily disposal rate of $T_4$-I which averaged 43.7±7.3 μg/day.

During the entire period of acute malarial infection, values for TDS did not change appreciably and averaged 8.54±1.77 liters. Decreases in (k) during infection were observed whether patients were receiving methimazole (Fig. 1 *A* and *B*) or not (Fig. 2 *A* and *B*). Thus, during the period of acute illness, (k) averaged 6.4±1.7%/day which represented an increase in $T_4$ half-life of from 5.86 to 11.63 days. As would be expected, there were concomitant decreases in the $T_4$ clearance rate (0.55± 0.19 liters) and daily rate of disposal of $T_4$ (23.9±7.3 μg/day) during the period of infection.

During the convalescent period, values for TDS were again little changed and averaged 8.71±1.93 liters (mean ±SD), while values for (k) (12.8±2.2%/day), $T_4$ clearance rate (1.12±0.33 liters), and daily $T_4$ disposal rate (53.8±21.4 μg/day), all returned to the ranges observed during the initial control period.

*Concentration of free and total $^{127}I$-$T_4$.* Values obtained for per cent free $T_4$ or concentration of free $T_4$ ($AFT_4$) showed little change during acute infection, and the $AFT_4$ was significantly greater than control only during convalescence (Table II, Fig. 3). Total serum $^{127}I$-$T_4$ and the total extrathyroidal $T_4$ pool tended to increase late in the infected period, and in five subjects who did not receive methimazole, were significantly greater during the convalescent period than in the preceding two periods. (Tables I and II). Values for total $^{127}I$-$T_4$ in the two subjects (F. W. and D. G.) who were receiving methimazole tended to decrease during the latter days of the study. Consequently, data based on stable $T_4$ measurements in these subjects during convalescence were not analyzed together with that of the other six subjects. Nevertheless, it was observed that estimates for clearance and daily disposal of $T_4$ still increased over the values obtained during acute infection in these two subjects.

*Ratio of $PB^{131}I$: $^{127}I$-$T_4$ (Table III).* This ratio describes a slope with time relating values for the concentration of administered $^{131}I$-$T_4$ which reflect peripheral turnover, to values for the serum concentration of stable $T_4$ reflecting thyroidal secretion, and thus constitutes a form of specific activity expression (10). During the control period, the numerical value of the ratio (per cent dose per microgram) decreased exponentially with time, since $^{127}I$-$T_4$ remained constant and $PB^{131}I$ declined exponentially. In the six patients studied without methimazole blockade, the slope of the ratio with time averaged 12.8±0.7%/day. In five of the six patients the slopes decreased markedly during the acute illness period, and averaged 8.7±2.2%/day for all six subjects. During convalescence, the slope of the ratio increased with time, averaging 12.6±1.4%/day in the five patients

TABLE I

*The Effect of Experimental Falciparum Malaria Infection on Various Aspects of the Peripheral Metabolism of $T_4$ as Assessed after Administration of $^{131}I$–$T_4$*

| No. | Subject | Age | Weight | Experimental period | Study interval | Volume of distribution | $T_4$-I clearance rate | Fractional rate of $T_4$-I disappearance | $t_{\frac{1}{2}}$ | No. points $^{131}I$-$T_4$ | No. determinations $T_4$-I | Mean $T_4$-I | Extrathyroidal $T_4$-I concentration | Absolute $T_4$-I disposal rate |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *yr* | *lb.* | | *days* | *liters* | *liters/day* | *%/day* | *days* | | | *μg/100 ml* | *μg* | *μg/day* |
| 1 | E. B. | 46 | 193 | Control | 9.5–13.0 | 11.05 | 1.45 | 13.1 | 5.29 | 8 | 5 | 3.7 | 409 | 53.6 |
| | | | | Infected | 16.0–19.5 | 10.88 | 0.75 | 6.9 | 10.04 | 12 | 5 | 4.4 | 479 | 33.0 |
| | | | | Convalescent | 21.0–23.5 | 10.85 | 1.32 | 12.2 | 5.68 | 6 | 6 | 5.3 | 578 | 70.5 |
| 2 | R. F. | 18 | 165 | Control | 9.5–13.0 | 8.70 | 1.19 | 13.7 | 5.06 | 8 | 6 | 4.5 | 392 | 53.7 |
| | | | | Infected | 16.5–19.5 | 8.21 | 0.57 | 7.0 | 9.90 | 10 | 7 | 4.8 | 394 | 27.6 |
| | | | | Convalescent | 20.5–23.5 | 8.07 | 1.15 | 14.3 | 4.85 | 7 | 8 | 5.9 | 476 | 68.1 |
| 3 | A. T. | 20 | 122 | Control | 9.5–13.0 | 5.71 | 0.94 | 16.4 | 4.23 | 8 | 8 | 4.5 | 257 | 42.1 |
| | | | | Infected | 15.0–18.5 | 5.51 | 0.26 | 4.8 | 14.43 | 10 | 6 | 4.4 | 242 | 11.6 |
| | | | | Convalescent | 20.5–23.5 | 5.58 | 0.57 | 10.2 | 6.79 | 7 | 8 | 5.0 | 279 | 28.4 |
| 4 | K. T. | 22 | 135 | Control | 9.5–13.0 | 10.53 | 1.04 | 9.9 | 7.00 | 8 | 8 | 4.6 | 484 | 47.9 |
| | | | | Infected | 16.5–19.5 | 11.02 | 0.42 | 3.8 | 18.24 | 10 | 6 | 4.8 | 529 | 20.1 |
| | | | | Convalescent | 21.0–23.5 | 11.32 | 1.56 | 13.8 | 5.02 | 6 | 6 | 5.5 | 623 | 85.9 |
| 5 | B. B. | 18 | 154 | Control | 10.5–15.0 | 7.94 | 0.84 | 10.6 | 6.54 | 10 | 6 | 4.9 | 389 | 41.2 |
| | | | | Infected | 21.0–25.5 | 7.96 | 0.48 | 6.1 | 11.40 | 14 | 9 | 5.0 | 398 | 24.3 |
| | | | | Convalescent | 27.0–30.0 | 8.40 | 0.88 | 10.5 | 6.60 | 7 | 6 | 5.5 | 462 | 48.5 |
| 6 | B. R. | 19 | 165 | Control | 10.5–15.0 | 8.33 | 0.86 | 10.3 | 6.73 | 10 | 8 | 4.3 | 358 | 36.9 |
| | | | | Infected | 25.5–29.0 | 8.69 | 0.70 | 8.0 | 8.66 | 12 | 10 | 4.2 | 365 | 29.2 |
| 7 | D. G.* | 27 | 145 | Control | 10.5–15.0 | 8.26 | 1.02 | 12.3 | 5.63 | 10 | 6 | 4.0 | 330 | 40.6 |
| | | | | Infected | 21.5–25.5 | 7.82 | 0.41 | 5.2 | 13.33 | 13 | 11 | 4.1 | 321 | 16.7 |
| | | | | Convalescent | 27.0–30.0 | 8.87 | 0.98 | 11.1 | 6.24 | 7 | 6 | 4.2 | 372 | 41.3 |
| 8 | F. W.* | 22 | 139 | Control | 10.5–15.0 | 9.80 | 1.06 | 10.8 | 6.42 | 10 | 6 | 3.2 | 314 | 33.9 |
| | | | | Infected | 19.5–25.5 | 8.23 | 0.81 | 9.8 | 7.07 | 17 | 10 | 3.6 | 296 | 29.0 |
| | | | | Convalescent | 27.0–30.0 | 7.88 | 1.36 | 17.2 | 4.03 | 7 | 6 | 2.5 | 197 | 33.9 |
| 1–6‡ | Mean ± SD | | | Control | | | | | | | | 4.4 ± 0.4 | 382 ± 74 | 45.9 ± 7.0 |
| | | | | Infected | | | | | | | | 4.7 ± 0.3 | 401 ± 99 | 24.3 ± 7.6 |
| | | | | Convalescent | | | | | | | | 5.2 ± 0.6 | 484 ± 133 | 60.3 ± 22 |
| 1–8 | Mean ± SD | | | Control | | 8.79 ± 1.68 | 1.05 ± 0.19 | 12.1 ± 2.2 | 1.86 ± 1.0 | | | 4.2 ± 0.5 | 367 ± 69 | 43.7 ± 7.3 |
| | | | | Infected | | 8.54 ± 1.77 | 0.55 ± 0.19 | 6.4 ± 1.7 | 11.63 ± 3.6 | | | 4.4 ± 0.4 | 378 ± 94 | 23.9 ± 7.3 |
| | | | | Convalescent | | 8.71 ± 1.93 | 1.12 ± 0.33 | 12.8 ± 2.2 | 5.60 ± 1.0 | | | 4.8 ± 1.1 | 427 ± 154 | 53.8 ± 21.4 |

* Subjects receiving methimazole (30 mg every 6 hr) during study.

‡ Mean ± SD for estimations of those data based on measurement of serum stable $T_4$-I in the patients not receiving methimazole.

TABLE II

*Effect of Experimental Falciparum Malaria Infection on Values for Free and Total Serum Thyroxine ($^{127}I$-$T_4$) in Normal Subjects**

| No. | Subjects | Period | Serum $^{127}I$-$T_4$ | Per cent free $T_4$ | Free $T_4$ concentration |
|---|---|---|---|---|---|
| | | | *μg/100 ml* | % | *ng/100 ml* |
| 1 | E. B. | Control | 3.7±0.2 | 0.019±0.000 | 1.1±0.1 |
| | | Infected | 4.3±0.4 | 0.019±0.002 | 1.3±0.2 |
| | | Convalescent | 5.3±0.4 | 0.018±0.000 | 1.4±0.1 |
| 2 | R. F. | Control | 4.5±0.5 | 0.015±0.000 | 1.1±0.1 |
| | | Infected | 4.9±0.3 | 0.016±0.002 | 1.2±0.1 |
| | | Convalescent | 5.6±0.3 | 0.018±0.001 | 1.5±0.1 |
| 3 | A. T. | Control | 4.5±0.4 | 0.018±0.001 | 1.2±0.1 |
| | | Infected | 4.4±0.2 | 0.021±0.004 | 1.4±0.3 |
| | | Convalescent | 4.7±0.4 | 0.020±0.001 | 1.4±0.1 |
| 4 | K. T. | Control | 4.6±0.4 | 0.019±0.003 | 1.4±0.3 |
| | | Infected | 4.8±0.4 | 0.020±0.002 | 1.5±0.2 |
| | | Convalescent | 5.5±0.3 | 0.019±0.000 | 1.5±0.1 |
| 5 | B. B. | Control | 4.9±0.3 | 0.019±0.001 | 1.5±0.1 |
| | | Infected | 5.0±0.3 | 0.020±0.002 | 1.6±0.2 |
| | | Convalescent | 5.5±0.2 | 0.019±0.000 | 1.6±0.1 |
| 6 | B. R. | Control | 4.3±0.5 | 0.023±0.001 | 1.5±0.2 |
| | | Infected | 4.2±0.1 | 0.022±0.001 | 1.4±0.1 |
| 7 | D. G.‡ | Control | 4.0±0.2 | 0.028±0.001 | 1.8±0.1 |
| | | Infected | 4.1±0.3 | 0.025±0.001 | 1.6±0.1 |
| | | Convalescent | 4.2±0.2 | 0.027±0.001 | 1.8±0.1 |
| 8 | F. W.‡ | Control | 3.2±0.3 | 0.026±0.002 | 1.3±0.1 |
| | | Infected | 3.6±0.4 | 0.038±0.004 | 2.0±0.4 |
| | | Convalescent | 2.5±0.6 | 0.041±0.004 | 1.5±0.4 |
| 1–6 | Mean±SEM§ | Control | 4.4±0.2 | 0.019±0.000 | 1.3±0.1 |
| | | Infected | 4.6±0.1 | 0.020±0.000 | 1.4±0.1 |
| | | Convalescent | 5.3±0.2 | 0.019±0.000 | 1.5±0.1 |

*Values represent mean±SD for all samples in which both total and free $T_4$ were determined.
‡ Subjects receiving methimazole (30 mg every 6 hr) during study.
§ Mean±SEM in subjects not receiving methimazole.

studied postinfection, as compared to an average of 8.8±2.8%/day in the same patients during acute illness. Typical curves for specific activity ratios obtained in three subjects in the absence of methimazole blockade are shown in Fig. 4. The changes observed in the slopes for the ratio during acute illness reflect the slowing in $^{131}I$-$T_4$ turnover seen during this period (Table I, Figs. 1 and 2), while the increasing slope during convalescence reflects the tendency to rising values for serum stable $T_4$ concentration during this study interval (Table II, Fig. 3).

*Ratio of $PB^{131}I$: $PB^{125}I$.* This ratio is a variety of specific activity expression similar to the ratio $PB^{131}I$: $^{127}I$-$T_4$, in that the concentrations of both $^{127}I$-$T_4$ and $PB^{125}I$ represent endogenously released hormonal iodine. Changes in the slope of the ratio with time thus reflect alterations in the magnitude of peripheral $T_4$ turnover relative to the release of hormonal iodine from the thyroid. Calculated values for the ratio of $PB^{131}I$: $PB^{125}I$ decreased with time in all patients during the control period, and the slope averaged 0.133±0.011 (Table IV). Typical curves for the slope of this ratio throughout the five study periods are shown in Fig. 5. The slope of the ratio with time was little changed in the prodromal interval, but decreased significantly during the early half of the period of acute malarial infection, averaging for the group as a whole 0.075±0.012. Values for the slope of this ratio tended to increase again during the latter half of the acute infected period, presumably reflecting increasing $^{125}I$ release from the thyroid. This is also sug-

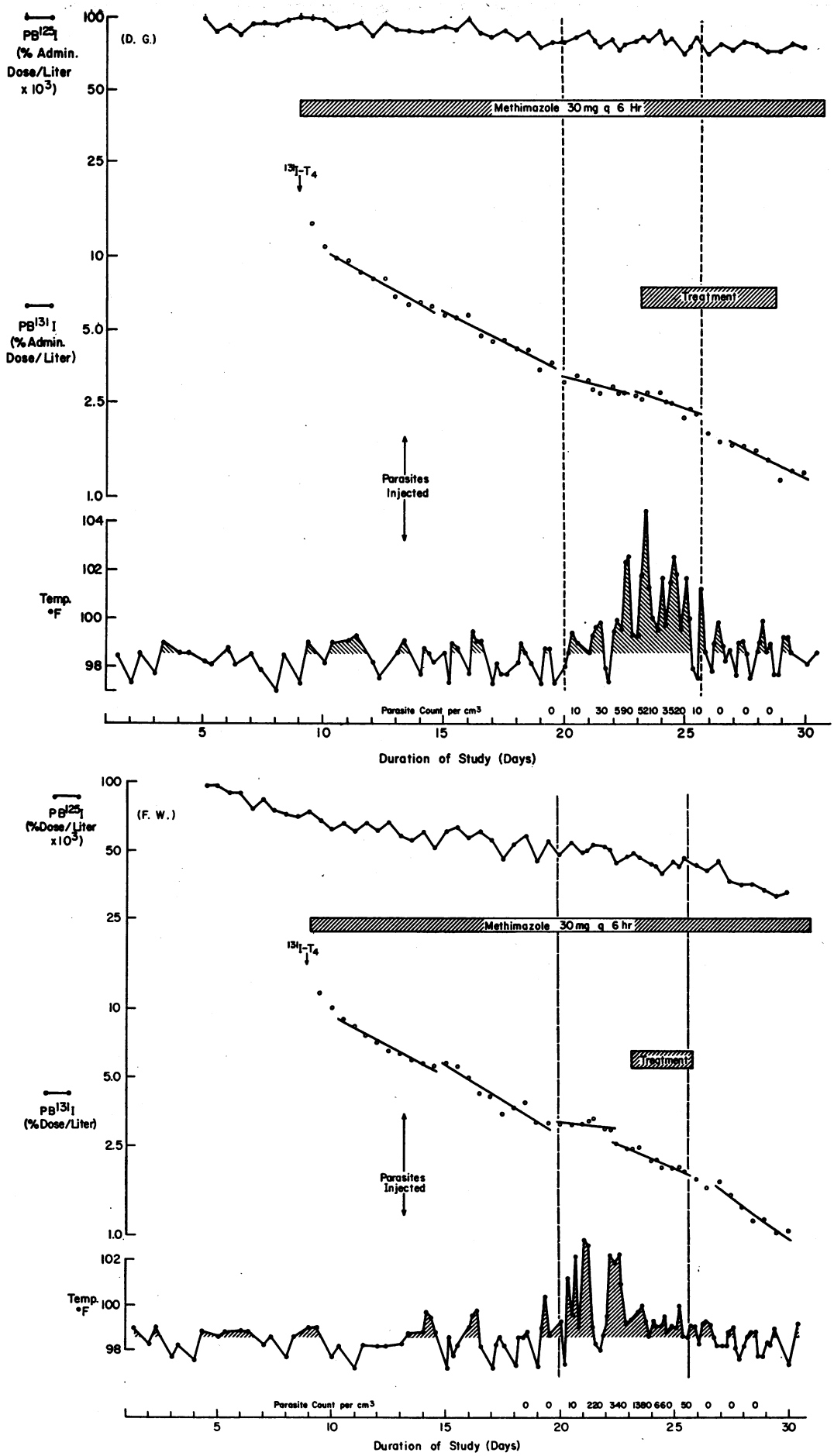
(D. G.)
PB125I (% Admin. Dose/Liter x 10³)
Methimazole 30 mg q 6 Hr
131I-T4
Treatment
PB131I (% Admin. Dose/Liter)
Parasites Injected
Temp. °F
Parasite Count per cm³ 0 10 30 590 5210 3520 10 0 0 0
Duration of Study (Days)
(F. W.)
PB125I (%Dose/Liter x10³)
Methimazole 30 mg q 6 hr
131I-T4
Treatment
PB131I (%Dose/Liter)
Parasites Injected
Temp. °F
Parasite Count per cm³ 0 0 10 220 340 1380 660 50 0 0 0
Duration of Study (Days)

FIGURE 1.

TABLE III

*Effect of Experimental Falciparum Malarial Infection on Thyroidal Release of $T_4$ as Assessed by the Slope with Time of the Ratio $PB^{131}I:{}^{127}I\text{-}T_4$*

| No. | Patient | Control period | | Acute infection | | Convalescence | |
|---|---|---|---|---|---|---|---|
| | | Slope ± SEE* | r‡ | Slope ± SEE | r | Slope ± SEE | r |
| 1 | E. B. | 0.118±0.061 | 0.93 | 0.153±0.067 | 0.91 | 0.080±0.033 | 0.90 |
| 2 | R. F. | 0.152±0.115 | 0.84 | 0.128±0.056 | 0.91 | 0.140±0.014 | 0.97 |
| 3 | A. T. | 0.113±0.038 | 0.97 | (+)0.014±0.042 | 0.25 | 0.165±0.040 | 0.96 |
| 4 | K. T. | 0.120±0.084 | 0.85 | 0.105±0.050 | 0.87 | 0.134±0.060 | 0.88 |
| 5 | B. B. | 0.118±0.072 | 0.93 | 0.068±0.089 | 0.58 | 0.113±0.048 | 0.90 |
| 6 | B. R. | 0.148±0.081 | 0.93 | 0.080±0.036 | 0.91 | — — — | — |
| 7 | D. G.§ | 0.108±0.030 | 0.97 | 0.066±0.055 | 0.79 | 0.117±0.033 | 0.95 |
| 8 | F. W.§ | 0.142±0.055 | 0.97 | 0.132±0.102 | 0.80 | (+)0.050±0.054 | 0.14 |
| 1–6 | Mean±SEM | 0.128±0.007 | | 0.087±0.022 | | 0.126±0.014 | |

* Standard error of estimate of the slope with time (fraction per day) of the $PB^{131}I/{}^{127}I\text{-}T_4$ ratio (per cent dose per microgram. For simplification the sign of values for the slopes is omitted, all values being negative but the two indicated.

‡ Correlation coefficient of the $PB^{131}I:{}^{127}I\text{-}T_4$ ratio vs. time.

§ Subjects receiving methimazole (30 mg every 6 hr) during period of study and not included in mean summation of slopes.

gested by a further rise in values for $PB^{125}I$ from those at the asymptote, which was seen in subjects not receiving methimazole (Fig. 2 *A* and *B*), and also by rapidly increasing urine $^{125}I/^{131}I$ ratios (see below). During the convalescent period, the slope of the curve describing this ratio was for the most part little changed or slightly decreased, averaging 0.097±0.005. This may be the result of some recycling to the thyroid and secondary release of $^{131}I$ generated from $^{131}I\text{-}T_4$ in the periphery in the six patients not receiving methimazole.

*Ratio of $U^{125}I:PB^{125}I$ and $U^{131}I:PB^{131}I$.* After the injection of $^{131}I\text{-}T_4$ or the endogenous release of $^{125}I\text{-}T_4$, inorganic I* liberated by peripheral deiodination of $T_4$ accumulates in the thyroid or is excreted in the urine. The rate of generation of I*, and its rate of entry into these two sites of disposal, is proportional to the plasma $T_4$-I*

TABLE IV

*Effect of Experimental Falciparum Malaria Infection on Thyroidal Release of $T_4$ as Assessed by the Slope with Time of the Ratio $PB^{131}I:PB^{125}I$*

| No. | Subject | Control period | | Prodrome | | Early acute infection | | Late acute infection | | Convalescence | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Slope± SEE* | r‡ | Slope± SEE | r | Slope± SEE | r | Slope± SEE | r | Slope± SEE | r |
| 1 | E. B. | 0.162±0.046 | 0.96 | 0.159±0.026 | 0.96 | 0.065±0.090 | 0.46 | 0.080±0.015 | 0.77 | 0.076±0.026 | 0.91 |
| 2 | R. F. | 0.149±0.049 | 0.96 | 0.174±0.025 | 0.98 | 0.054±0.097 | 0.37 | 0.113±0.031 | 0.82 | 0.110±0.047 | 0.87 |
| 3 | A. T. | 0.128±0.046 | 0.94 | 0.298±0.056 | 0.96 | 0.100±0.025 | 0.87 | 0.199±0.081 | 0.81 | 0.096±0.033 | 0.93 |
| 4 | K. T. | 0.160±0.049 | 0.96 | 0.115±0.047 | 0.87 | 0.087±0.033 | 0.89 | 0.267±0.035 | 0.97 | 0.110±0.055 | 0.91 |
| 5 | B. B. | 0.124±0.041 | 0.97 | 0.088±0.033 | 0.97 | 0.105±0.038 | 0.88 | 0.106±0.028 | 0.93 | 0.096±0.039 | 0.93 |
| 6 | B. R. | 0.154±0.055 | 0.97 | 0.110±0.047 | 0.98 | 0.121±0.040 | 0.92 | 0.132±0.018 | 0.98 | — — | — |
| 7 | D. G.§ | 0.110±0.043 | 0.96 | 0.075±0.022 | 0.98 | 0.029±0.028 | 0.64 | 0.054±0.042 | 0.73 | 0.111±0.047 | 0.92 |
| 8 | F. W.§ | 0.075±0.072 | 0.80 | 0.092±0.060 | 0.91 | 0.039±0.044 | 0.54 | 0.080 0.041 | 0.88 | 0.078±0.041 | 0.88 |
| 1–8 | Mean±SEM‖ | 0.133±0.011 | | 0.139±0.026 | | 0.075±0.012 | | 0.129±0.025 | | 0.097±0.005 | |

* Standard error of estimate of the slope with time (fraction per day) of the $PB^{131}I:PB^{125}I$ ratio (per cent dose/per cent dose).

‡ Correlation coefficient of the $PB^{131}I:PB^{125}I$ ratio vs. time.

§ Subjects receiving methimazole (30 mg every 6 hr) during study.

‖ Mean±SEM for slope with time of $PB^{131}I:PB^{125}I$ in all eight subjects.

FIGURE 1 The effect of malarial infection on the thyroidal release and peripheral metabolism of $T_4$ in two normal subjects (D. G. and F. W.) receiving methimazole 30 mg every 6 hr. Patients were given inorganic $^{125}I$ followed by $^{131}I\text{-}T_4$ several days later. Serial measurements were made of serum protein-bound $^{125}I$ and $^{131}I$.

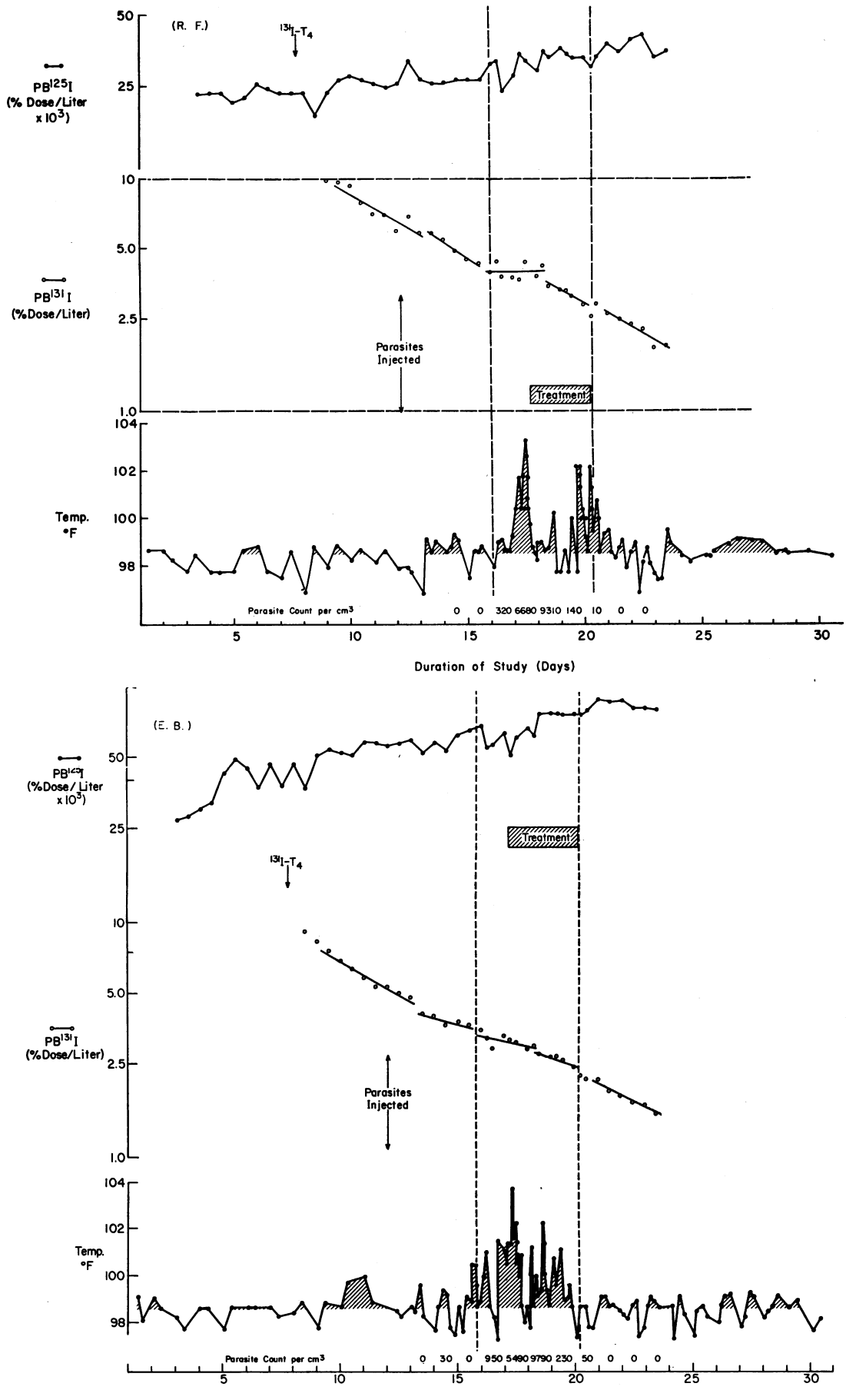
(R. F.)
$^{131}I$-$T_4$
$PB^{125}I$ (% Dose/Liter x $10^3$)
$PB^{131}I$ (%Dose/Liter)
Parasites Injected
Treatment
Temp. °F
Parasite Count per cm$^3$ 0 0 320 6680 9310 140 10 0 0
Duration of Study (Days)
(E. B.)
$PB^{125}I$ (%Dose/Liter x $10^3$)
$PB^{131}I$ (%Dose/Liter)
$^{131}I$-$T_4$
Parasites Injected
Treatment
Temp. °F
Parasite Count per cm$^3$ 0 30 0 950 5490 9790 230 50 0 0 0
Duration of Study (Days)

FIGURE 2.

concentration. Therefore, provided that the fractional rate of $T_4$ deiodination is unchanged, the quotient of the rate of increase in thyroidal plus urinary I* and the plasma $T_4$-I* concentration should remain constant with time. Since this quotient reflects the quantity of $T_4$ deiodinated per unit time relative to the quantity of $T_4$ in the plasma available for deiodination, it has been termed the "deiodinative clearance" of $T_4$ (17, 18). If the thyroid is accumulating I*, only a fraction of the total deiodinative clearance of $T_4$ is reflected in urinary I* excretion, and normally this fraction is constant. Hence, the ratio of urinary I* excretion rate and plasma $T_4$-I* concentration will remain constant with time under steady-state conditions. It is, in fact, a "partial" deiodinative clearance rate, representing that portion of the total deiodinative clearance that is reflected in urinary I* excretion.

Values for $U^{125}I:PB^{125}I$ and $U^{131}I:PB^{131}I$ ratios with time, based upon 12-hr urine collections were examined throughout the entire period of study (Table V). The two patients who received methimazole are not included in this analysis, since values for these ratios would be increased by methimazole administration to a greater degree immediately after initial blockade than later, thus exaggerating any changes observed during infection (18). Values for $U^{125}I:PB^{125}I$ tended to decrease from a control value of 1.319±0.304 liters (mean±SE), progressively during the period of prodrome (1.088±0.280 liters) to reach a nadir during the early half of the

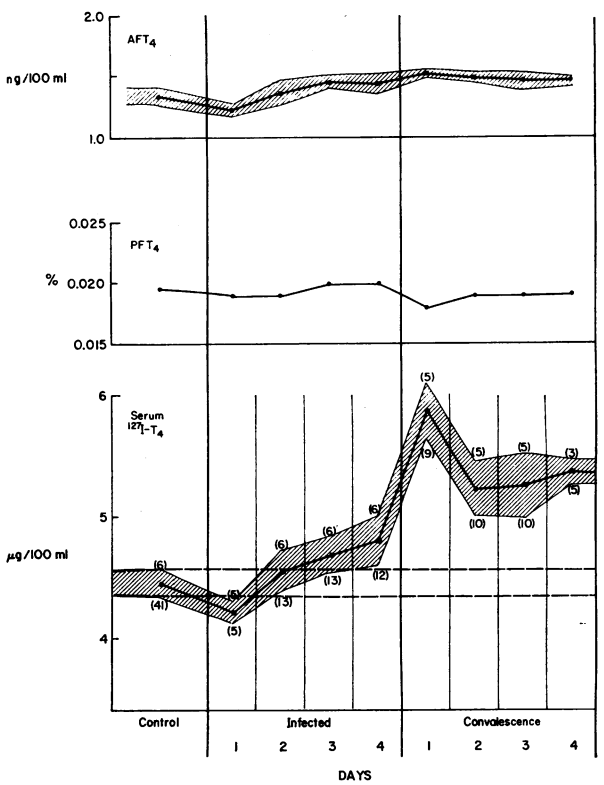


FIGURE 3 The effect of acute malarial infection on values for serum total thyroxine ($^{127}I$-$T_4$), per cent free thyroxine ($PFT_4$), and the absolute concentration of free $T_4$ ($AFT_4$). Figures in upper bracket represent number of patients studied; lower bracket the total number of determinations. Values are mean ±SEM.

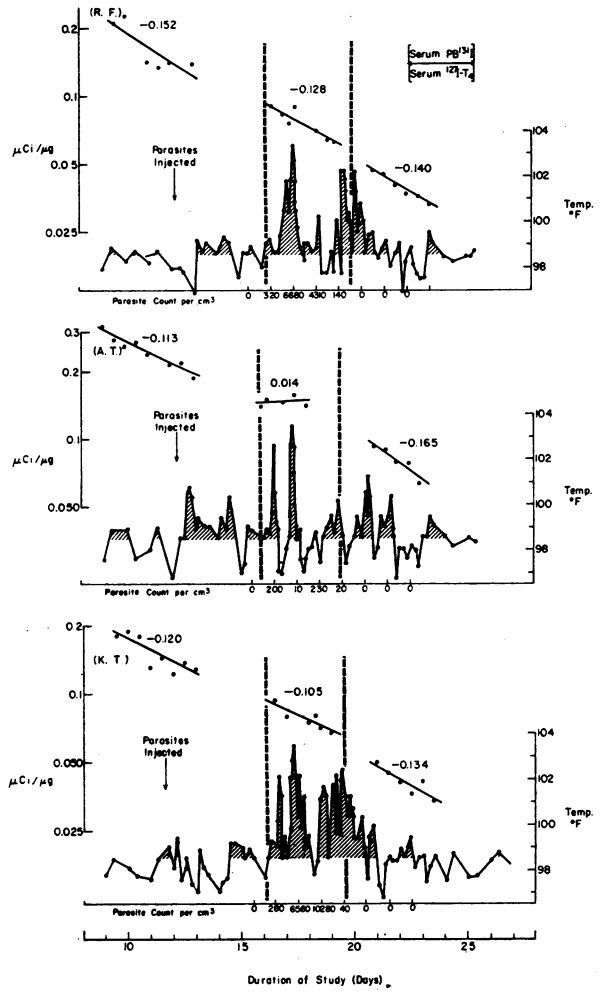


FIGURE 4 The effect of acute malarial infection on thyroidal $T_4$ release in three normal subjects as judged from the ratio of serum $PB^{131}I$ to $^{127}I$-$T_4$ concentrations. Regression slopes for the ratio are shown for control, infected, and convalescent periods. Patients received intravenous $^{131}I$-labeled $T_4$.

FIGURE 2 The effect of malarial infection on the thyroidal release and peripheral metabolism of $T_4$ in two normal subjects (R. F. and E. B.). Patients were given inorganic $^{125}I$ followed by $^{131}I$-$T_4$ several days later. Serial measurements were made of serum protein-bound $^{125}I$ and $^{131}I$.

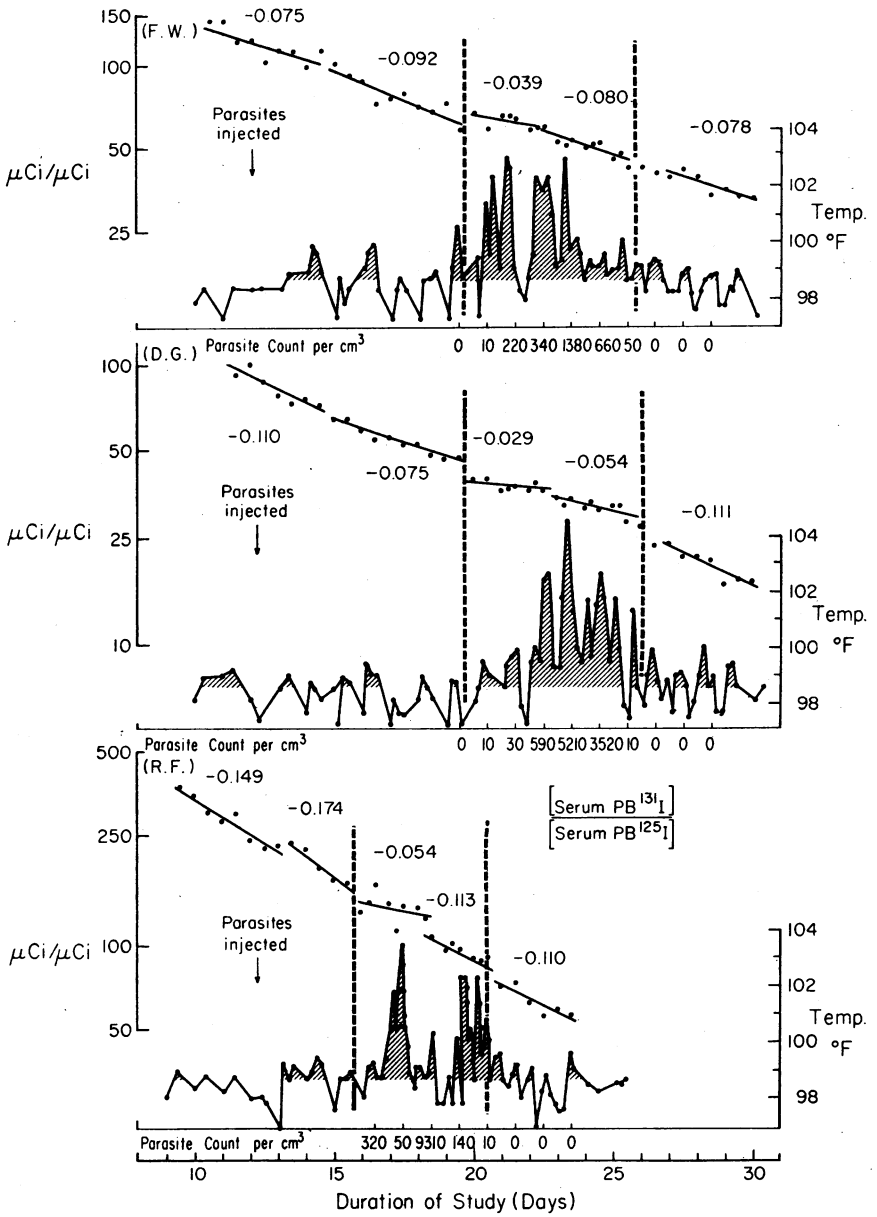


FIGURE 5 The effect of acute malarial infection on thyroidal $T_4$ release in three normal subjects as judged from the ratio of the concentrations of serum $PB^{131}I$ to $PB^{125}I$. Two of these subjects (F. W. and D. G.) received methimazole blockade. Patients received inorganic $^{125}I$ followed by $^{131}I$-labeled $T_4$.

period of acute illness (0.697±0.117) liters. Subsequently, values for $U^{125}I : PB^{125}I$ increased in the latter half of the acute illness period (0.879±0.162 liters) and remained so throughout the period of convalescence (0.900±0.182 liters). There were variable to slight decreases in values for $U^{131}I/PB^{131}I$ during infection, but the major alterations were seen to affect $U^{125}I/PB^{125}I$ ratios (Table V).

*Ratio of $U^{125}I : U^{131}I$.* After the administration of $^{125}I$ to label thyroidal iodine, and $^{131}I$-$T_4$ to label the extrathyroidal thyroxine pool, values for the ratio of $^{125}I : ^{131}I$ in urine pass through equilibratory and transition phases before assuming a progressively rising slope, said to represent $^{125}I$ release from the thyroid (11). In the steady state, urinary radioiodine derived from peripheral $^{131}I$-$T_4$ changes at a relatively constant rate, and any changes in

TABLE V

*Effect of Experimental Falciparum Malaria Infection on Deiodinative Clearance Rates for $T_4$ as Assessed by Values for the Ratio $U^{125}I:PB^{125}I$ and $U^{131}I:PB^{131}I$ after Injection of $^{125}I$ and $^{131}I - T_4$**

| No. | Subject | Ratio | Control period | Prodrome | Early acute infection | Late acute infection | Convalescence |
|---|---|---|---|---|---|---|---|
| 1 | E. B. | $U^{125}I:PB^{125}I$ | 1.323±0.262 | 1.123±0.117 | 0.826±0.143 | 1.025±0.345 | 0.990±0.283 |
| | | $U^{131}I:PB^{131}I$ | 0.350±0.070 | 0.434±0.056 | 0.413±0.053 | 0.360±0.122 | 0.343±0.036 |
| 2 | R. F. | $U^{125}I:PB^{125}I$ | 2.289±0.522 | 2.202±0.758 | 1.018±0.348 | 1.224±0.741 | 1.278±0.424 |
| | | $U^{131}I:PB^{131}I$ | 0.339±0.057 | 0.436±0.147 | 0.312±0.093 | 0.326±0.154 | 0.318±0.109 |
| 3 | A. T. | $U^{125}I:PB^{125}I$ | 1.244±0.644 | 0.900±0.130 | 0.517±0.275 | 0.641±0.233 | 0.629±0.191 |
| | | $U^{131}I:PB^{131}I$ | 0.265±0.109 | 0.310±0.033 | 0.209±0.087 | 0.282±0.073 | 0.260±0.076 |
| 4 | K. T. | $U^{125}I:PB^{125}I$ | 2.040±0.859 | 1.484±0.427 | 0.999±0.349 | 1.412±0.504 | 1.260±0.259 |
| | | $U^{131}I:PB^{131}I$ | 0.348±0.139 | 0.371±0.098 | 0.361±0.120 | 0.417±0.181 | 0.428±0.061 |
| 5 | B. B. | $U^{125}I:PB^{125}I$ | 0.519±0.226 | 0.379±0.213 | 0.381±0.156 | 0.508±0.120 | 0.341±0.174 |
| | | $U^{131}I:PB^{131}I$ | 0.234±0.089 | 0.248±0.139 | 0.243±0.084 | 0.296±0.077 | 0.190±0.077 |
| 6 | B. R. | $U^{125}I:PB^{125}I$ | 0.498±0.118 | 0.441±0.064 | 0.438±0.099 | 0.463±0.062 | — |
| | | $U^{131}I:PB^{131}I$ | 0.288±0.037 | 0.335±0.059 | 0.376±0.066 | 0.349±0.061 | — |
| 7 | D. G.‡ | $U^{125}I:PB^{125}I$ | 0.791±0.436 | 0.811±0.472 | 0.802±0.249 | 0.846±0.198 | 1.188±0.515 |
| | | $U^{131}I:PB^{131}I$ | 0.261±0.144 | 0.275±0.150 | 0.296±0.113 | 0.358±0.70 | 0.249±0.084 |
| 8 | F. W.‡ | $U^{125}I:PB^{125}I$ | 1.501±0.591 | 1.144±0.407 | 1.138±0.458 | 1.284±0.322 | 0.754±0.351 |
| | | $U^{131}I:PB^{131}I$ | 0.522±0.201 | 0.470±0.155 | 0.504±0.130 | 0.545±0.183 | 0.416±0.142 |
| 1–6§ | Mean±SE | $U^{125}I:PB^{125}I$ | 1.319±0.304 | 1.088±0.280 | 0.697±0.117 | 0.879±0.162 | 0.900±0.182 |
| | | $U^{131}I:PB^{131}I$ | 0.304±0.017 | 0.356±0.028 | 0.319±0.032 | 0.338±0.017 | 0.308±0.039 |

* Values for the ratio $U^{125}I:PB^{125}I$ or $U^{131}I:PB^{131}I$ are mean±SD expressed as liters per 12 hr.

‡ Subjects receiving methimazole (30 mg every 6 hr) during study.

§ Mean±SE in all subjects not receiving methimazole.

the slope of $U^{125}I:U^{131}I$ thus reflect alterations in thyroidal iodine release, which are in turn mediated via changes in TSH secretion (20). Values for this ratio abruptly declined with the onset of fever and infection (Fig. 6), only to rise rapidly with treatment and resume the control "release" slope in the convalescent period. This sequence parallels the changes in serum concentrations of $PB^{125}I$ and $^{127}I$-$T_4$ described above (Tables III and IV, Fig. 3), and suggests an initial inhibition of hormonal release followed by a rebound phase of accelerated release.

Of particular interest is the one patient (F. W.) whose malarial infection was not cured by a single course of drug therapy. This patient relapsed some 2 wk after conclusion of the study, with recurrent low grade fever and parasitemia requiring further treatment. An examination of values for the ratio of $U^{125}I:U^{131}I$ in this subject revealed that the initial depression from the basal release slope during infection was not followed by a rebound to the control slope as seen in all the other patients. Rather, it was observed that the ratio remained depressed throughout the duration of the study (Fig. 7). There possibly existed then, a state of more "chronic" infection that was marked by continued inhibition of release of hormonal iodine ($PB^{125}I$). This could account for the declining values of $^{127}I$-$T_4$ observed during the "convalescence" of this subject, particularly in view of the administered methimazole blockade.

*Effect of WR-30090 alone.* The antimalarial compound WR-30090 was administered in the usually employed dosage to two volunteers not infected with malaria, but otherwise studied as described above. No significant changes were observed during drug administration in any of the various parameters reflecting either thyroidal release of endogenous $^{125}I$, e.g. ratios of $U^{125}I:U^{131}I$, or of the peripheral metabolism of the exogenous $^{131}I$-labeled $T_4$. Values for the fractional disappearance rate for $T_4$ (per cent/day) during control, drug therapy, and posttreatment control periods, were for the first subject: 10.3±6.0, 11.0±3.9, and 9.0±7.9; and for the second subject: 9.3±5.4, 10.2±4.3, and 7.3±5.0, respectively (mean ±SD).

*Simultaneous $^{125}I$-$T_4$ and $^{131}I$-$T_4$ turnover during infection.* In two subjects the double isotope technique as employed above was not used, but rather a single injection of $^{125}I$-$T_4$ was given initially, followed by the usual injection of malarial parasites. At the first sign of infection, a second injection of $T_4$ labeled with $^{131}I$ was given, and simultaneous fractional turnover rates were determined. This was done in an attempt to demonstrate that the observed decrease in turnover during infection was not a function of time, recycling of radioiodine and its

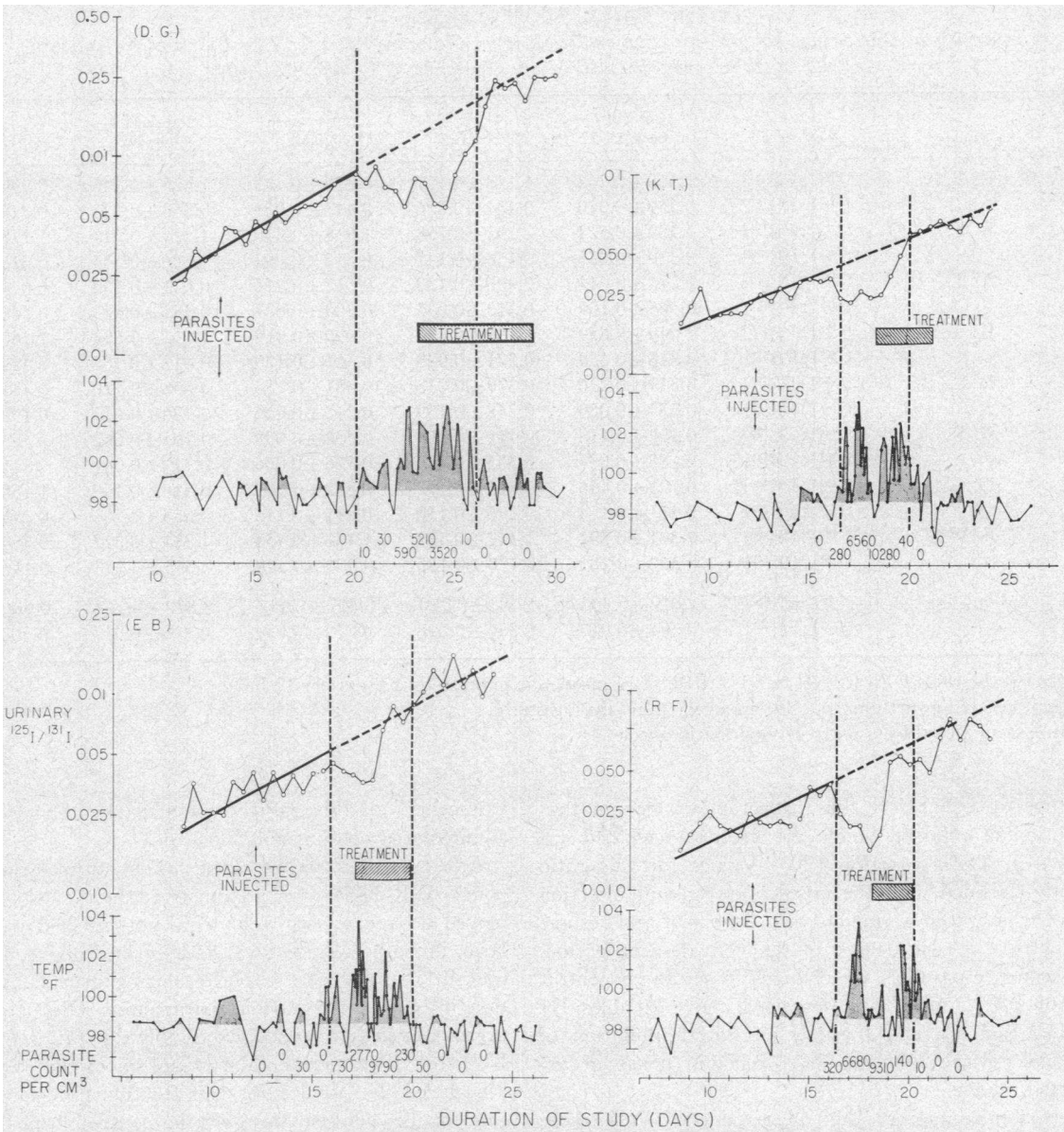


FIGURE 6 The effect of acute malarial infection on thyroidal release of $T_4$ in four normal subjects as judged by values for the ratio of $U^{125}I:{}^{131}I$. The solid line represents the calculated control "release" slope. The patients were given inorganic $^{125}I$ followed several days later by $^{131}I$-$T_4$.

secondary release, or other factors. Only one of these subjects developed clinical infection. The individual who did not become ill (M. S.) was therefore never given an injection of $^{131}I$-$T_4$. The slope of values for $^{125}I$-$T_4$ with time, as well as urine $^{125}I:PB^{125}I$ ratios are shown to illustrate their relative constancy in this subject who received parasites but did not develop clinical infection (Fig. 8). Observations in the other patient, who did become sick (B. N.), revealed no significant differences between the fractional turnover rates for $^{125}I$-$T_4$ and $^{131}I$-$T_4$. Likewise, values for their respective deiodinative clearances could be virtually superimposed (Fig. 9).

## DISCUSSION

Studies of thyroid function during infection in animals and man have yielded a variety of results. The preponderance of data, however, suggests that peripheral thyroxine ($T_4$) turnover is increased (1–5), and that thy-

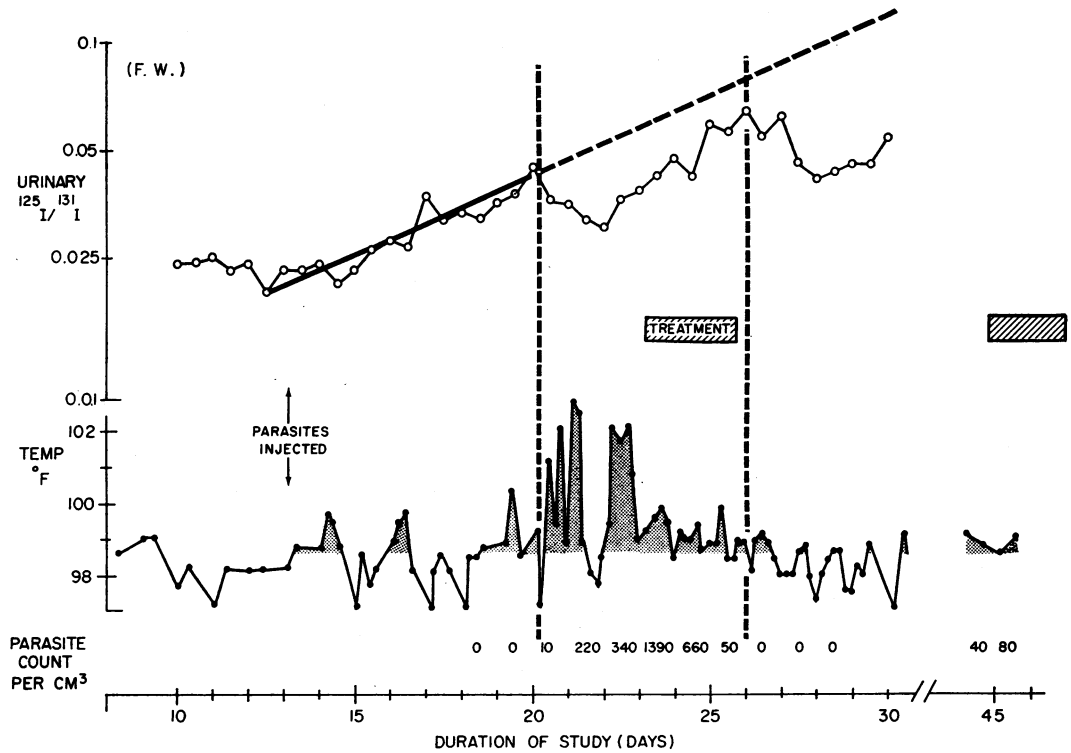


FIGURE 7 The effect of acute and "chronic" malarial infection on thyroidal release of $T_4$ in a normal subject. Note the failure of values for $U^{125}I:{}^{131}I$ to regain the control release slope after antimalarial therapy, and the recurrence of parasitemia 2 wk later.

roid function is generally depressed initially, and then often rebounds during recovery from the infectious illness (6–9). The great majority of these earlier studies depended either upon the use of epithyroid counting to estimate the rate of release of glandular hormonal iodine, or upon measurement of the concentration of serum $PB^{131}I$ with time after the injection of labeled $T_4$, in order to assess peripheral $T_4$ metabolism.

The double isotope technique utilized in the present study is free of many of the shortcomings of serial epithyroid counting as an index of hormonal release, and allows the simultaneous analysis of both the secretion of thyroid hormone and the peripheral turnover of $T_4$ (10). In the study of thyroid function during acute malaria, the method has generated observations which agree in certain aspects with earlier results in other infections but for one striking disparity, the finding of a decreased, rather than an accelerated rate of $T_4$ removal. In earlier studies, an increase of the fractional rate of $T_4$ turnover [(k)] has been observed during infectious illness in rats (2), monkeys (5), and man (1, 3, 4), although Wiswell and Coronho noted no change in $T_3$ turnover in volunteers given typhoid fever (21). A decrease in $T_4$ turnover has been observed only after surgical stress (22, 23).

Gregerman and Solomon (3) described an increase of (k) in 26 of 33 patients with pneumonias, which were predominantly pneumococcal. $T_3$ turnover, in contradistinction to Wiswell's findings, was also increased in six subjects. These workers invoked an increase in thyroidal secretion of $T_4$ during acute infection, in view of an increased (k) in the face of no change in $T_4$ distribution space or PBI. However, an enhanced rate of $T_4$ secretion is not supported by studies demonstrating suppressed thyroidal $^{131}I$ release during infection in various species (2, 3, 24–26), or by ratios for urinary $^{125}I/^{131}I$ in the present study (Fig. 6), which indicate inhibition of hormonal release. Lutz, Hornick, Dawkins, and Gregerman (4) reported an increased (k) in one of five volunteers given typhoid fever, two of five given malaria, and in none of five given tularemia. With the data now available, we are unable to account satisfactorily for the disparity between their results in the malaria-infected subjects and the decrease in (k) seen in the present study. Most recently, studies of thyroid function during pneumococcal infection in monkeys, using an essentially identical isotope technique to that employed in the present study, have shown acceleration of both $T_3$ and $T_4$ turnover. An increased clearance rate and daily disposal of $T_4$ during acute illness was also seen, with return to control values during convalescence (5).

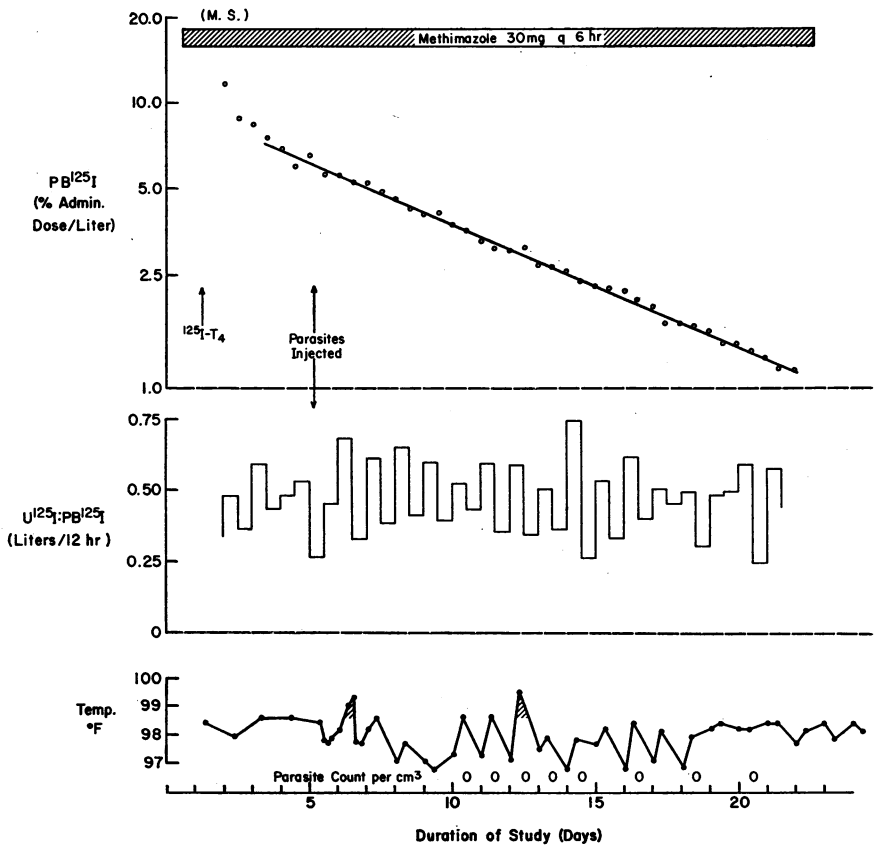


FIGURE 8 The lack of detectable alterations in the peripheral metabolism of $T_4$ in a normal subject who failed to develop clinical infection after administration of malarial parasites. Values are shown for serum concentrations of $PB^{125}I$ and the ratio of $U^{125}I : PB^{125}I$ after injection of thyroxine-$^{125}I$.

Because of the evidence for increase in (k) during infection, we have attempted to examine critically the decrease of $T_4$ turnover seen in the present study. Conceivably, water loss from fever, coupled with decreased fluid intake, may have led to hemoconcentration with a consequent artifactual slowing in $^{131}I$-$T_4$ disappearance. This is considered unlikely since values for the concentration of serum $^{127}I$-$T_4$ decreased rather than increased as one would have predicted with hemoconcentration, and no change was noted in estimates of $T_4$ distribution space. In this regard, studies of fluid compartmentalization during acute falciparum malaria have revealed that vasodilation occurs, with increases in plasma volume secondary to a compensatory shift of fluid into the vascular space (*27*). This might lead to a shortened $T_4$ half-life during acute infection, which makes the observation of a decreased $T_4$ turnover even more remarkable.

The validity of the present observations is strengthened somewhat by the fact that values for rates of fractional turnover, clearance, and daily disposal of $T_4$ all returned to their preinfection control ranges during convalescence. The increase in (k) during convalescence was observed even in the patients not receiving methimazole (Fig. 2 *A* and *B*). This observation is noteworthy since the curve describing the disappearance of $PB^{131}I$ from serum may by this time show a slowing, owing to the accumulation and secretion by the thyroid of radioiodine originating from peripheral degradation of the $^{131}I$-$T_4$ (1).

Examination of the changes during infection in the slopes with time of the ratio $PB^{131}I : {}^{127}I$-$T_4$ or $PB^{131}I : PB^{125}I$ provides another means of analysis of thyroid hormone economy. Although no additional independent measurements are performed, analysis by this method lends support to the validity of the alterations in rates of peripheral $T_4$ disposal and thyroidal iodine release as assessed individually by other methods.

Further evidence of a decrease in $T_4$ turnover and thyroid iodine release may be obtained by examining urine : plasma iodine ratios during infection. Values for $U^{125}I : PB^{125}I$ were clearly depressed during acute illness (Table V) while those for $U^{131}I : PB^{131}I$ showed only minor decreases. Although we cannot determine from the present

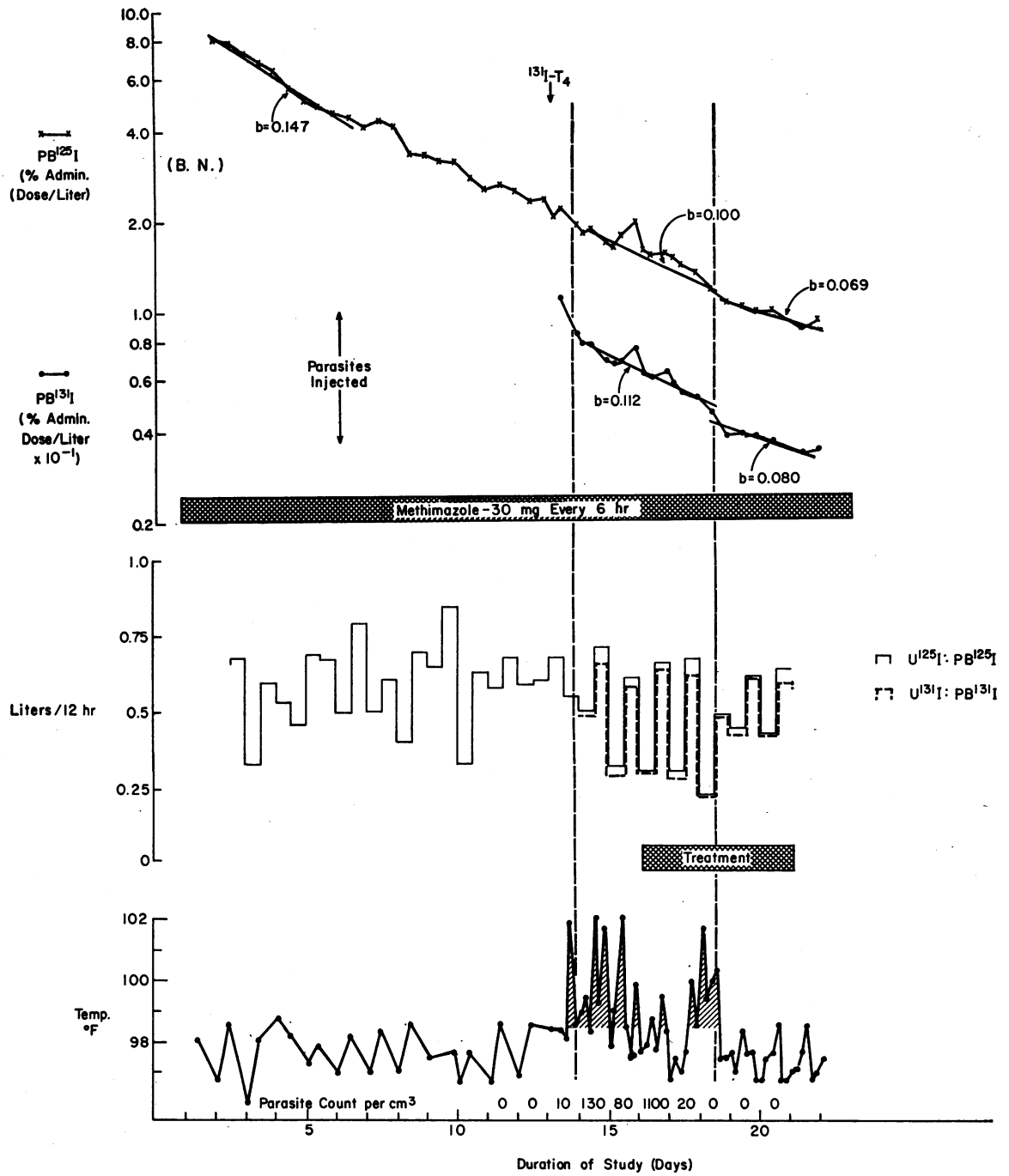


FIGURE 9 Similarities between the peripheral metabolism of $^{125}$I-T$_4$ and $^{131}$I-T$_4$ during acute malarial infection in a normal subjects. Patient was given $^{125}$I-T$_4$ followed later by $^{131}$I-T$_4$ at first sign of clinical illness.

data why $U^{131}I : PB^{131}I$ did not decrease in the face of a decrease in (k), some tentative explanations may be inferred. First, the occurrence of a greater decrease in the ratio $U^{125}I : PB^{125}I$ might be predicted, since a decrease in urinary $^{125}$I could represent the combined effect of a slowing in peripheral degradation of $PB^{125}I$, as well as decreased release of hormonal and nonhormonal $^{125}$I from the thyroid. Secondly, studies demonstrating that

epinephrine produces a decrease in (k) lead us to speculate that a catecholamine excess accompanying acute infectious illness could contribute to the observed changes in $T_4$ metabolism. In addition to a decreased (k), these workers found evidence for decreased fecal clearance of $T_4$-$^{131}I$ (28). The latter catechol effect, together with impairment in liver excretory function during acute malaria, could produce a decreased hepatobiliary excretion of $T_4$. A decreased fecal clearance, with the possibility of a hormonal shift from the hepatic compartment to blood, could result in increased generation of $^{131}I$ into the urine, so that values for $U^{131}I : PB^{131}I$ might not decrease. Fecal $^{131}I$ or $^{125}I$ was not determined in the present study, and this question remains unresolved. A decreased fecal $T_4$ clearance alone could not fully account for the observed decrease in (k) however, since only approximately 20% of $T_4$ disposal is by this route (14).

Lastly, a decreased fractional uptake of $^{131}I$ (RAIU) could also play some role in maintaining higher than predicted ratios of $U^{131}I : PB^{131}I$, at least in the subjects not receiving methimazole. There is ample evidence that the RAIU is depressed in a variety of animal species during acute stress due to infection, bacterial toxins, and other related noxious stimuli (2, 25, 29–31). Under these circumstances, the fraction of $^{131}I$ derived from the peripheral deiodination of $^{131}I$-$T_4$ and which ordinarily would have been trapped by the thyroid, would consequently enter the urine. If the thyroidal uptake were completely inhibited, urinary radioiodine from this source would increase by a factor of 100/100-RAIU. This factor, together with possible changes in fecal disposal, could perhaps account for the failure of values for $U^{131}I : PB^{131}I$ to decrease during acute illness despite a decreased fractional disappearance rate for $^{131}I$-$T_4$.

Studies in rodents (2) and man (4, 8, 32) have indicated that significant increases in the per cent of free $T_4$ ($PFT_4$) occur during infection. Since these increases have occurred in association with decreases in PBI, the concentration of free hormone ($AFT_4$) in serum has been generally normal to slightly increased. The reason for the absence of a significant increment in $PFT_4$ or $AFT_4$ during the acute infectious phase of the present study is unclear. The lack of induction of a decrease in $T_4$ binding may be specific to malarial infection, or related to severity of clinical illness and fever. Our patients did not become as sick nor as febrile as those given malaria by Lutz for example (4), and a correlation between temperature and $PFT_4$ has been shown in vitro (33, 34). Failure of the $AFT_4$ to rise is not necessarily causally related to the absence of an increase in (k) during infection, since little relation may exist between (k) and the $FT_4$ in some circumstances (4), and because cellular factors may be more important determinants of $T_4$ turnover than is the $FT_4$ (35).

Observations in animals, of a decreased serum PBI during acute infection followed by a later rebound, are compatible with the transient depression of thyroidal $^{131}I$ release rates observed in these species (2, 5, 6, 24–26). Modest decreases in PBI have been observed during infection in man as well, again often demonstrating a rise to normal limits or greater during recovery (4, 8–9). In the present study, the observed changes in $^{127}I$-$T_4$ after the onset of acute malaria (Table II, Fig. 3) agree in substance with these earlier reports.

As has been detailed above, there is a substantial body of data that supports either increases or decreases in $T_4$ turnover during acute stress and infection. We propose that the disparity between those studies suggesting an increased $T_4$ turnover and the present study is related to the specific hepatotoxicity of acute malaria. Although liver involvement in falciparum malaria is well recognized (36–40), the degree of clinically detectable hepatic dysfunction may depend on whether the infection is naturally acquired or experimentally induced. Sadun, Williams, and Martin found liver function abnormalities in servicemen with naturally acquired disease, but no consistent abnormalities despite marked parasitemia, in normal volunteers given parasitized red blood cells in much the same way as in the present study. They did note elevations in serum transaminase (SGOT and SGPT) in chimpanzees similarly infected however, and concluded that serious disturbances of liver function occur during either naturally acquired or artificially induced malaria (36). This has also been suggested by Maegraith who described the histopathologic appearance of the liver in acute falciparum malaria as one of congestion, with centrilobular degeneration and necrosis (37). Further, even the presumption of minimal exoerythrocytic infection after artificial induction of malaria does not preclude toxic effects on the liver, since there is evidence for circulating histotoxins which cause fatty degeneration of parenchymal cells and inhibition of mitochondrial respiratory processes (41, 42). Changes have also been demonstrated in hepatic cellular cations, with an increase in water content consistent with the effect of a circulating toxin, detrimental to cell membranes (43).

Development of hepatic dysfunction during malarial infection is relevant to $T_4$ metabolism, since marked prolongation of $T_4$ disappearance rates have been described in the presence of liver disease (44, 45). Oppenheimer, Bernstein, and Hasen proposed that changes in (k) were related to changes in the tissue $T_4$ compartment as well as to determinants of plasma protein binding. The transfer kinetics of rapidly exchangeable intracellular $T_4$ were examined in patients with liver disease by the use of differentially labeled $T_4$ and albumin. A decreased fractional transfer from extracellular to cellular compartments was demonstrated, which resulted in decreased intracellular

accumulation of $T_4$. These abnormalities were attributed to changes in hepatic cellular permeability, due either to aberrations in membrane porosity or the $T_4$ transport mechanism (35). Thus, a decreased hepatocellular uptake of $T_4$ might constitute the mechanism underlying decreased $T_4$ turnover during acute malaria. Employing techniques similar to those of Oppenheimer, other workers have assessed rapid cellular uptake in monkeys during pneumococcal disease, and found evidence for enhanced cellular uptake of $T_4$, supporting their own observations of increased $T_4$ turnover in this infection (5, 46). The disparity in the results of $T_4$ turnover rates between the present study and those examining pneumococcal infection in monkeys might be resolved by an examination of thyroid function after induction of the same infections in the converse experimental model, e.g., pneumococcal infection in man or falciparum malaria in the monkey. Such studies could, perhaps, further clarify the role of the liver in the peripheral metabolism of the thyroid hormones during infection.

Finally, an examination of urine ratios of $^{125}I/^{131}I$ (Fig. 6) clearly confirms the marked, although transient, depression in thyroidal release occurring during acute illness. This phenomenon has been observed previously in one patient during stress and infection by Nicoloff (11). This method of assessing thyroidal iodine release depends upon generation of $^{131}I$ from peripheral $^{131}I$-$T_4$ at a relatively constant rate, so that changes in the $U^{125}I : U^{131}I$ ratio reflect alterations in endogenous $^{125}I$ secretion. It should be apparent that the turnover of $PB^{131}I$ is altered during infection so that it could no longer be said to serve as a constant reference source for peripheral deiodination. A depression in the slope of the $U^{125}I : U^{131}I$ ratio during infection is therefore even more striking, since the observed slowing in fractional turnover of $^{131}I$-$T_4$ should generate less urinary $^{131}I$, and thereby increase rather than decrease values for this ratio.

These observations suggest that the sequence of events during infection with malaria may be an initial, immediate depression of thyroidal release followed by a compensatory phase of accelerated hormonal secretion. There are a number of studies which suggest by indirect methods an inhibition of thyrotrophin (TSH) release by fever or stress (11, 26, 47). Kohler, O'Malley, Rayford, Lipsett, and Odell reported a suppression of immunoassayable TSH in three hypothyroid subjects after administration of pseudomonas pyrogen (Piromen) (48). On hypothetical grounds, an inhibitory effect of fever or infectious toxins acting at the level of the hypothalamus would seem likely, and other evidence suggests that this suppression is cortisol mediated (20, 49). Although the present study allows some insight into alterations in peripheral $T_4$ metabolism and the response of the pituitary-thyroid axis to infection, further investigations will be required to clarify the nature of these interactions.

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