THYROGLOBULIN IN SERUM AFTER I\textsuperscript{131} THERAPY

I. SALTING OUT*

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(Received for publication, August 12, 1953)

The normal serum iodine appears to consist largely of thyroxine (1, 2), in loose combination with a specific protein carrier (3). Although other iodine-containing substances may also be present (4, 5) and may have considerable physiological importance (6), these contribute only a small proportion of the total serum iodine at any one time. Attempts to demonstrate thyroglobulin in serum by immunological methods have been unsuccessful, unless the blood was taken directly from the thyroid vein during mechanical trauma to the thyroid gland (7, 8).

After the administration of large doses of radioiodine, however, considerable amounts of an abnormal serum iodine component may be found, coincident with an abrupt loss of I\textsuperscript{131} from thyroid tissue (9, 10). Studies on patients (10) and on rats (11) have indicated that this material resembles thyroglobulin in its insolubility in n-butanol, its behavior on chromatographic analysis, and its iodinated amino acid composition, as well as in its electrophoretic mobility at pH 8.6 (12). Proof of the nature of this compound, however, has been lacking.

To characterize this abnormal serum iodine component further, its behavior has been studied during salting out of the serum proteins with phosphate buffer and during sedimentation of the serum proteins in the ultracentrifuge. The data to be presented in this, and in the succeeding paper (13), are more direct evidence that the material entering the circulation during irradiation of thyroid tissue, is, in fact, thyroglobulin.

Materials and Methods

Thirteen patients were studied: one who received I\textsuperscript{131}-labeled L-thyroxine intravenously, and the others, after oral "therapeutic" doses of

* This work was supported by a grant from the Damon Runyon Memorial Fund for Cancer Research, a grant from the American Cancer Society, and a contract with the Atomic Energy Commission, No. AT(30-1)-910.

\textsuperscript{1} Radioiodide (I\textsuperscript{131}) was obtained from Oak Ridge and was administered with less than 10 \(\gamma\) of carrier iodide. L-Thyroxine was obtained through the courtesy of the Smith, Kline and French Laboratories and was labeled with I\textsuperscript{131} by Dr. G. Gleason of the Abbott Laboratories. It was approximately 90 per cent pure by chromato-
radioiodide of varying amounts. Pertinent information for each patient is recorded in Table I. A measure of the approximate radiation delivered to thyroid tissue in each patient was estimated by methods previously described (10). Butanol solubility of serum $^{131}$I was determined either by direct extraction of serum (10) or after precipitation of the serum protein with trichloroacetic acid (11). Radioactivity was measured with a $\gamma$-ray counter; either a sensitive Texas Company Geiger-Müller tube or a well type scintillation counter was used.

Paper chromatographic analysis of serum $^{131}$I was performed by techniques described earlier (10, 12). The three solvent systems employed are indicated in Table I. By the use of whole serum in these analyses, it was possible to observe the behavior of all the serum $^{131}$I components (11). The percentage of the total $^{131}$I in each radioactive band was estimated by measuring the area under the graph depicting net radioactivity.

Salting out curves for serum protein in the presence of phosphate buffer, pH 6.5, were obtained by a modification of the methods of Derrien (16, 17). Dilutions of a stock buffer solution (an equimolecular mixture of KH$_2$PO$_4$ and K$_2$HPO$_4$, 3.5 M) were prepared in centrifuge tubes so that the addition of 1 ml. of a 1:3 dilution of serum to 9 ml. of the salt mixtures resulted in phosphate buffer concentrations ranging from 1.19 to 2.975 M (34 to 85 per cent$^2$). In this way, the final serum dilution remained constant at 1:30. Increments in phosphate buffer concentration of 0.07 to 0.175 M (2 to 5 per cent$^2$) were used. The pH of the buffer-serum mixtures, measured with a Beckman pH meter, was 6.55 ± 0.05 over the concentration range employed.

The contents of the tubes were mixed by inversion and allowed to stand for approximately 16 hours in an incubator at 23-25$^\circ$. The flocculent precipitate was then separated by the ether-centrifugation method of Kingsley (18). Evidence against the production of artifacts due to denaturation of protein was obtained by (1) the similarity in results when filtration was used to remove the precipitate (Cases 2 and 10), and (2) the similarity of the zone electrophoretic pattern (pH 8.6) of redissolved precipitate (2.975 M) to that of untreated serum. The ether layer did not contain significant amounts of $^{131}$I.

Aliquots of the aqueous phase were used to measure radioiodine or protein remaining in solution at each salt concentration. A duplicate tube at 1.19 M phosphate buffer was used as a standard, representing total radioiodine or protein, by omitting the ether-centrifugation step and shaking graphic analysis. Cohn Fractions II and V of human plasma were kindly supplied by Dr. S. T. Gibson and Dr. J. N. Ashworth of the American National Red Cross and E. R. Squibb and Sons, respectively.

$^2$ Per cent by volume of the stock buffer solution.
well before aliquots were taken. The small amount of precipitate in the standard redissolved during preparation of the sample for protein analysis.

Radioiodine in 5 ml. aliquots was measured with a γ-ray counter of the type noted above. Protein was determined by ultraviolet absorption at 275 μm (19) and by biuret analysis. In the latter, the method of Weichselbaum (20) was modified by adding 1 ml. of 10 N NaOH (carbonate-free) to the unknown-reagent mixture, since color otherwise failed to develop. Blank corrections were made from a plot of optical density versus concentration at several phosphate buffer dilutions, since this relationship was not linear. Color development followed Beer's law over the concentration range encountered, and biuret analysis of Cohn Fractions II and V of human plasma revealed identical optical density-nitrogen ratios. A plot of these data was used for the determination of total serum protein in whole serum. (Nitrogen was measured by the micro-Kjeldahl technique).

Purified human thyroglobulin, labeled with I\textsuperscript{131}, was prepared from 5 gm. of normal thyroid tissue removed from a 75 year-old man during total laryngectomy for laryngeal carcinoma. The patient had been given 2 mc. of radioiodide 48 hours prior to surgery. The gland was frozen immediately upon excision, and purified thyroglobulin was prepared according to the methods of Derrien et al. (21) with equimolecular KH\textsubscript{2}PO\textsubscript{4} and KH\textsubscript{2}PO\textsubscript{4}. The final precipitate was dialyzed against water so that the final product (total weight 54 mg.) contained approximately 0.02 mM of the phosphate buffer; it was then lyophilized.

Chromatographic analysis of the purified thyroglobulin in the butanol-dioxane-ammonia system revealed that all of the radioiodine remained at the origin. In the crude thyroid extract, 4 per cent of the I\textsuperscript{131} behaved like iodide.

Ultracentrifugal analysis\textsuperscript{3} of a 1 per cent solution of the purified human thyroglobulin in 0.2 M NaCl showed that 83 per cent of it was in a single sharp boundary, with a sedimentation constant of \( s_{20,w} = 17.6 \) S. 11 per cent sedimented at a faster rate and 6 per cent more slowly.

Electrophoretic analysis of the purified thyroglobulin by the moving boundary technique,\textsuperscript{3} with barbital buffer, pH 8.6, ionic strength 0.1, revealed a single component with a mobility of \( -5.4 \times 10^{-5} \) cm\textsuperscript{2} per second per volt. In the presence of diluted plasma (2 gm. of plasma protein per 100 ml.) the mobility of purified thyroglobulin was \( -4.8 \times 10^{-5} \) cm\textsuperscript{2} per second per volt and was intermediate between those of α\textsubscript{1}- and α\textsubscript{2}-globulin. Zone electrophoretic analysis in filter paper (with the same buffer) of mixtures of crude thyroid extract or of purified thyroglobulin, with

\textsuperscript{3} The author is indebted to Dr. M. L. Petermann for these determinations. Ultracentrifugal analysis was performed with the Spinco model E ultracentrifuge by the optical method.
Table I
Summary of Clinical Data; Butanol Solubility and Chromatography of Serum \( ^{131}I \)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Clinical data*</th>
<th>( ^{131}I ) dose</th>
<th>Approximate radiation to thyroid tissue in 2nd 24 hrs.</th>
<th>Time of sample after dose</th>
<th>BrOH-soluble ( ^{131}I )</th>
<th>Chromatography</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mc.</td>
<td>rep  β</td>
<td>days</td>
<td>per cent of total</td>
<td>per cent of total</td>
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<td></td>
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<td></td>
<td></td>
<td>Thyroxine ( ^{131}I )</td>
<td>Origin ( ^{131}I )</td>
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<td>Group A. Serum ( ^{131}I ) largely thyroxine</td>
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<td></td>
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<tr>
<td>1</td>
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<td>(5 min.)</td>
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<td>95§</td>
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<tr>
<td>2</td>
<td>Graves' disease</td>
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<td>1,600</td>
<td>4</td>
<td>75.5∥</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>&quot; &quot;</td>
<td>15</td>
<td>2,700</td>
<td>4</td>
<td>72.8∥</td>
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<tr>
<td>4</td>
<td>&quot; &quot;</td>
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<td>5,300</td>
<td>5</td>
<td>85.3‡</td>
<td>9</td>
</tr>
<tr>
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<td>5,200</td>
<td>4</td>
<td>76.4‡</td>
<td>4</td>
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<td>6</td>
<td>Thyroid carcinoma</td>
<td>53</td>
<td>17,000</td>
<td>7</td>
<td>71.7∥</td>
<td>4</td>
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<td></td>
<td>Normal thyroid present</td>
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<td></td>
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<td>Non-functioning metastases</td>
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<tr>
<td>8</td>
<td>Thyroid carcinoma</td>
<td>200</td>
<td>5,800</td>
<td>7</td>
<td>92.7‡</td>
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<td>Group B. Serum ( ^{131}I ) largely abnormal</td>
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<tr>
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<td>23,000</td>
<td>5</td>
<td>53.0‡</td>
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<td>Thyroid carcinoma</td>
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<td>15,000</td>
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<td>26.0∥</td>
<td>32‡</td>
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<tr>
<td></td>
<td>Non-functioning metastases</td>
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<tr>
<td>11</td>
<td>Thyroid carcinoma</td>
<td>180</td>
<td>17,000</td>
<td>6</td>
<td>42.5‡</td>
<td>32‡</td>
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<tr>
<td></td>
<td>Functioning metastases</td>
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<tr>
<td>12</td>
<td>Thyroid carcinoma</td>
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<td>16,000</td>
<td>9</td>
<td>28.9‡</td>
<td>15‡</td>
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<td></td>
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<td>8</td>
<td>28.6‡</td>
<td>9**</td>
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<td></td>
<td></td>
<td>9§</td>
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<tr>
<td></td>
<td>Functioning metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8†</td>
</tr>
</tbody>
</table>

* Of the subjects listed as "athyreotic," Case 8 had had a total surgical thyroidectomy and had negligible uptake of \( ^{131}I \) in the neck; the others had received one or more large doses of \( ^{131}I \) (> 75 mc.) at least several months prior to this study.

† L-Thyroxine, 0.1 mg.

‡ Trichloroacetic acid method of extraction.
serum, indicated that more than 90 per cent of the radioactivity moved in a single band with a similar mobility. The remaining activity was streaked from the origin to the major band.

Mixtures containing 1.0 and 0.05 mg. of purified thyroglobulin per ml. of normal serum and 0.017 ml. of crude thyroid extract per ml. of serum were prepared and subjected to the salting out procedure. Specific activity calculations indicated that the latter mixture contained approximately 0.15 mg. of thyroglobulin per ml. of serum.

Results

The results of butanol extraction and chromatographic analysis of the serum radioiodine (Table I) allowed the separation of the patients into two groups: Group A, those whose serum I$^{131}$ behaved largely like thyroxine, and Group B, those whose serum I$^{131}$ included large amounts of an abnormal component; i.e., iodine-containing material which was insoluble in butanol and remained at the origin in the various chromatographic systems. Except in two instances, this abnormal finding could be correlated with the approximate radiation delivered to thyroid tissue (10).

The similarity in results obtained with the various chromatographic systems employed is illustrated by Cases 8 and 13. In one patient with functioning thyroid carcinoma and no normal thyroid tissue (Case 8), a small amount of serum I$^{131}$ with the same $R_F$ as triiodothyronine was found on the butanol-dioxane-ammonia chromatogram, and its presence was confirmed by radioautography. A similar finding is recorded in Paper II (Case 13b).

The chromatographic data (Table I) indicate that the sera contained varying amounts of radioiodide. When comparisons were available, it was found that these values were close to those for I$^{131}$ soluble in 2.975 m phosphate buffer. (The latter values were usually 1 to 5 per cent higher.) At this phosphate concentration, 96 to 99.5 per cent of the serum protein had been precipitated. In two sera more than 15 per cent of the I$^{131}$ was "non-precipitable" (Case 5, 29 per cent; Case 9, 40 per cent). Since the

4 Recovery experiments with radioiodide added to normal serum indicated that 90 per cent of the I$^{131}$ remained in solution in 2.975 m phosphate buffer.
values for total $I^{131}$ solubility at all salt concentrations are raised by the presence of soluble radioiodide, it was necessary to correct the data for this factor when interpreting the salting out curves of "protein-bound" $I^{131}$. To accomplish this, an arbitrary value of 5 per cent $I^{131}$ solubility at 2.975 M was adopted for each serum, and all other values were adjusted accordingly. The data obtained in this manner are illustrated in Fig. 1.

The mean salting out curve for sera containing largely "thyroxine $I^{131}$" (Fig. 1, Group A) reveals that somewhat more than half of the radio-

![Diagram](https://via.placeholder.com/150)

**Fig. 1.** Salting out curves for serum "protein-bound $I^{131}$" and for thyroglobulin. • represents the mean salting out curve for the sera of Group A ("thyroxine-$I^{131}$"); ○ represents purified human thyroglobulin in normal serum (1.0 mg. per ml.). The salting out curves for all sera of Group B ("abnormal $I^{131}$ component") fall within the dotted area.

iodine precipitated at phosphate buffer concentrations greater than 2.3 M, the remainder precipitating, in a gradual fashion, at lower concentrations. The salting out of serum $I^{131}$ in Group B, however, was quite different, owing to precipitation of large amounts of radioiodine between 1.40 and 1.75 M phosphate buffer. The standard deviation from the mean solubilities in Group A ranged from 2.4 to 9.1 per cent of total $I^{131}$. Mean solubilities for Group B were not calculated, since these sera contained variable amounts of the abnormal component. There was no overlapping of individual values in the two groups between 1.6 and 2.3 M phosphate buffer.

The salting out curves for serum protein were comparable to those obtained by Derrien (16), and the mean curves for the sera of Group A and
Group B were identical. The total serum protein was also the same for both groups (the mean for all sera was 7.5 gm. per 100 ml., with a range of 6.6 to 8.4 gm.).

The salting out curve for purified human thyroglobulin in serum is also presented in Fig. 1. The three thyroglobulin-serum mixtures showed similar curves, with the exception that 14 per cent of the radiiodine in the crude thyroid extract was soluble at 1.75 M phosphate buffer and 6 per cent at 2.975 M. It is apparent that the solubility characteristics in phosphate buffer of the abnormal I\textsuperscript{131} component in Group B are similar to those of thyroglobulin. Derivative curves revealed that the maximal I\textsuperscript{131} precipitation occurred, in every instance, between 1.57 and 1.65 M phosphate buffer.

Quantitative estimates of "thyroglobulin I\textsuperscript{131}" in the sera of Group B might be obtained from the various procedures which have been described. Thus, "thyroglobulin I\textsuperscript{131}" would be equivalent to (1) immobile I\textsuperscript{131} in the chromatograms; (2) the butanol-insoluble I\textsuperscript{131}, after correction for unextracted iodide and thyroxine (10 per cent for the trichloroacetic acid method, 20 per cent for the direct method); and (3) the I\textsuperscript{131} insoluble in 1.75 M phosphate buffer after correction for precipitated thyroxine (30 per cent). In the latter two, thyroxine and iodide may be estimated by chromatography. When such considerations were applied to the sera of Group B, it was found that "thyroglobulin I\textsuperscript{131}" estimates ranged from 29 to 82 per cent of the total serum I\textsuperscript{131} by chromatography, 39 to 69 per cent by butanol extraction, and 22 to 57 per cent by salting out. In most instances the amount estimated by salting out was lowest. While such discrepancies might be inherent in the techniques employed, it is also possible that they might indicate the presence in serum of yet another iodine-containing material which remains at the origin on chromatography, which is partially soluble in n-butanol, and which has salting out characteristics more like that of serum albumin. Such a substance has been found in the serum of several patients with functioning thyroid carcinoma (22), but it is impossible to determine from the present data whether such material is indeed present in the serums of Group B.

Discussion

The solubility characteristics of human thyroglobulin in phosphate buffer appear to be similar to those obtained by Derrien et al. (21) for other mammalian thyroglobulins (hog, beef, horse, and dog). Strict comparisons are not possible, however, since the present studies were carried out on thyroglobulin-serum mixtures. Roche et al. (23) have shown that the salting out curve of hog thyroglobulin (in ammonium sulfate) is altered somewhat by the presence of serum, but the main characteristics of the
THYROGLOBULIN IN SERUM. I

curve remain unchanged. With the techniques used in the present study, thyroglobulin components of slightly differing solubilities, such as have been described for other mammalian thyroglobulins (21), would not have been detected.

Although the thyroglobulin concentration in the mixtures reported here was considerably lower than that employed by Roche et al., the lowest was still 95 per cent precipitable in 1.75 M phosphate buffer. In the sera of patients, however, the thyroglobulin concentration would have been even lower than in any of the artificial mixtures. The maximal increase in serum stable protein-bound iodine (measured by a modification of Barker's method (24)) which was observed after the doses of $^{131}I$ in Group B was approximately 10 $\gamma$ per 100 ml. Assuming this increase to be thyroglobulin iodine only and the iodine content of thyroglobulin to be 0.5 per cent, the maximal thyroglobulin concentration in serum would have been approximately 0.02 mg per ml. With these very small concentrations of thyroglobulin, a larger proportion of "thyroglobulin $^{131}I$" might remain in solution at 1.75 M phosphate buffer. The specific activity of the purified thyroglobulin preparation, however, did not permit testing of this possibility.

An additional consideration might apply to patients receiving thiouracil derivatives, since thyroglobulin prepared from dogs receiving such drugs was found to be considerably more soluble in ammonium sulfate than was normal dog thyroglobulin (23). Only Case 11 had received thiouracil prior to the present study.

Although the above factors might have affected the determination of "thyroglobulin $^{131}I$" (see "Results"), it appears clear from the data presented that the abnormal serum iodine component could be characterized by the salting out procedure.

It is of interest to examine the salting out curve of serum $^{131}I$ when this was comprised largely of "thyroxine $^{131}I$" (Group A), since this would reflect the behavior of the protein to which thyroxine is attached. Derrien and Harboe (25) have defined the protein components in the various areas of the salting out curve of horse serum, demonstrating that $\gamma$-globulin precipitates below 1.5 M phosphate buffer, albumin above 2.3 M, and the $\alpha$- and $\beta$-globulins at intermediate concentrations. Thus, the present findings are in keeping with earlier studies, which indicated that more than half of the serum iodine was contained in the "albumin" fraction obtained by ammonium sulfate fractionation (26), or in Fractions V and VI, by Cohn's methods. Fraction IV (1, 27) and Fraction VI-3 (28), however, have considerably higher iodine-protein ratios, and zone electrophoretic analysis has revealed that about 85 per cent of the normal serum iodine has a discrete mobility intermediate between that of $\alpha_1$- and $\alpha_2$-globulins at pH 8.6 (3, 12, 29, 30).
The failure to demonstrate a sharply defined radioiodine component in the salting out curves of sera containing "thyroxine I\(^{131}\)" may be due to coprecipitation of the "thyroxine-binding protein" with other serum proteins under the conditions employed. It may also be that the "thyroxine-binding protein" resembles other serum proteins in that it salts out over a wide range of salt concentration. Thyroglobulin, on the other hand, has an extremely steep salting out curve, and this characteristic probably accounts for the ease with which the latter material was detected in the abnormal serums.

**SUMMARY**

The serum I\(^{131}\) has been examined following intravenous administration of labeled L-thyroxine in one patient and after oral administration of radioiodide for therapeutic purposes in twelve patients. In eight, the serum I\(^{131}\) was contained largely in thyroxine, as demonstrated by its solubility in \(n\)-butanol and its behavior in certain chromatographic systems. In five patients there was an abnormal serum I\(^{131}\) component, which was insoluble in butanol and immobile in the chromatographic systems.

The serum I\(^{131}\) was studied further by salting out of the serum proteins with equimolecular KH\(_2\)PO\(_4\) and K\(_2\)HPO\(_4\), pH 6.5. Those sera containing largely "thyroxine I\(^{131}\)" failed to reveal a radioiodine component with sharply defined solubility characteristics, while in the sera containing the abnormal material a large proportion of the radioactivity was precipitated between 1.40 and 1.75 M phosphate buffer concentration. Comparison of the abnormal iodine-containing material in serum with human thyroglobulin prepared from a normal thyroid gland demonstrated the similarity of these substances with regard to their solubility characteristics in phosphate buffer. Taken in conjunction with other observations, these data suggest that destruction of thyroid tissue with radioiodine may result in the release of unchanged thyroglobulin into the circulation.

The solubility characteristics of human thyroglobulin in phosphate buffer resemble those of other mammalian thyroglobulins.

The author wishes to acknowledge the most helpful advice and interest of Dr. Rulon W. Rawson, Dr. J. E. Rall, and Dr. Mary L. Petermann in this work. He is indebted, also, to Miss Helen Hagopian for technical assistance.

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