Clinical Investigation of the Physiologic Disposition of a Phthalanilide (NSC-38280) and a Phthalamidine Derivative (NSC-57155) in 7 Patients

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SUMMARY

Findings on blood levels, absorption and excretion of C¹⁴-labeled 4',4''-bis(2-imidazolin-2-yl)2-chloroterephthalanilide dihydrochloride (NSC-38280) after I. V. and P. O. administration, and on the quantitative and qualitative excretion of C¹⁴-labeled N,N''-bis[p-(N'-methylamidino)phenyl]terephthalamidine tetrahydrochloride (NSC-57155) after I. V. injection are presented. The half life in blood after I. V. infusion of NSC-38280 was 2 hr. and after I. V. injection of NSC-57155 approximately 45 min. Whereas only about 17 % of the activity of C¹⁴-NSC-38280 was excreted in urine within 6 days, the corresponding amount for C¹⁴-NSC-57155 was approximately 49 %. The excretion of radioactivity in feces within 6 days after administration of C¹⁴-NSC-57155 was only about 1 %. It was indicated that the excretion continues for many weeks after that period, and that the retained compound is partially stored in kidneys and liver. There was very little uptake of NSC-38280 by the gastrointestinal tract. These results are in accord with previously reported findings in rats.

Qualitative studies indicated that NSC-57155 is excreted in urine without change in the molecule, but in the form of a salt, conjugation product, or, most probably, a complex.

Following the intensive studies of the group of terephthalanilides (10) in animals (2—7, 9, 13, 15, 20, 21, 24, 28—31, 33, 34) and tissue culture (12, 23, 32), clinical trial of these compounds has been described by various investigators (16—18, 22). This report deals with the absorption and excretion of C¹⁴-labeled 4',4''-bis(2-imidazolin-2-yl)2-chloroterephthalanilide dihydrochloride (NSC-38280) after P. O. and I. V. administration, and with the quantitative and qualitative excretion of C¹⁴-labeled N,N''-bis[p-(N'-methylamidino)phenyl]terephthalamidine tetrahydrochloride (NSC-57155) after I. V. injection. The chemical structures of the 2 compounds are shown below:

![Chemical structures](image)

The asterisks indicate the C¹⁴-labeled atoms.

MATERIALS AND METHODS

Included in these studies were 5 children and 2 adult patients.

Five doses of 19—20 mg of C¹⁴-NSC-38280 (specific activity: 2.50 mc/mnmole) each were dissolved in 40 ml of pyrogen-free distilled water to which 0.03 ml of lactic acid (85 %) had been added. For 3 children receiving I. V. infusions over a 4-hr. period, this solution was diluted to 400 ml with 5 % glucose. Before, during, and after infu-
sion, samples of blood, urine, and spinal fluid (1 sample) were collected and their radioactivity checked (Table 1). For the 2 children receiving the drug P.O., the original solution of 40 ml was diluted with 20 ml of Lanolac and given in 1 dose, and with 20 ml of normal milk given in 2 doses at 5-min. intervals. Blood and urine samples were collected. For technical reasons, only incomplete stool samples could be obtained.

The drug dosage for all 5 patients was 0.9 mg/kg.

The 2 adult patients received I.V. injections of 1 mg/kg of C\textsuperscript{14}-NSC-57155 (specific activity: 0.7 mc/mmole and 0.525 mc/mmole, respectively) in a 16 % aqueous solution over a period of 15 min. Blood and urine samples were collected at various intervals, as indicated in Table 1. Also for technical reasons, stool samples could be obtained in total from only 1 patient. Two samples of expired air were collected from 1 patient.

**Laboratory Evaluations**

The radioactivity of most liquid samples was determined with the combustion method of Kalberer and Rutschmann (11). Stool samples were homogenized with water for 24 hr. and then lyophilized. An aliquot of the dry powder was combusted by the above-mentioned technic. Some samples were measured on planchets with a Baird atomic counter, model SA-302. The counts per minute (c.p.m.) per millilitre of blood, urine, and spinal fluid, or per milligrams of dried feces, were then divided by the drug's specific activity and expressed either in drug equivalents in \( \mu g/ml \) or % of the administered radioactivity, although no qualitative analysis was done in the C\textsuperscript{14}-NSC-38280 experiment.

Plasma and white and red blood cells were separated by the usual technic in a 3 % dextran solution. The samples of expired air were collected in 50 ml of absorption mixture as used for the combustion method.

Some blood and most urine samples of 1 patient receiving NSC-57155 were double-checked by a recently developed extraction procedure (14). This same procedure was used for the extraction of the compound from liver, kidneys, and abdominal fat tissue of an autopsied patient.

For the partition chromatography of urine, Celite 545,\textsuperscript{5} thoroughly washed with 6 N HCl, water, and alcohol and dried, was suspended in \( H_2O \)-saturated \( n \)-butanol and applied to a chromatography column 19 mm in diameter. This was then carefully stoppered with a Teflon stopper until a height of 410 mm was reached. The speed of the effluent was adjusted to approximately 8 drops/min. One-half gram of the lyophilized urine was mixed with a small amount of Celite 545 and \( H_2O \)-saturated \( n \)-butanol, then pressed on top of the column. Elution was performed with the same solvent, and fractions of 240 drops

\textsuperscript{5} Johns-Manville Corporation brand of diatomaceous earth.

### TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Blood (( \mu g/ml ))</th>
<th>Additional % of administered activity excreted in urine</th>
<th>Blood (( \mu g/ml ))</th>
<th>Additional % of administered activity excreted in urine</th>
<th>Blood (( \mu g/ml ))</th>
<th>Additional % of administered activity excreted in urine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time after</strong></td>
<td><strong>Patient 1</strong></td>
<td><strong>Patient 2</strong></td>
<td><strong>Patient 3</strong></td>
<td><strong>Time after</strong></td>
<td><strong>Patient 6</strong></td>
<td><strong>Patient 7</strong></td>
</tr>
<tr>
<td><strong>Start of Infusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 min.</td>
<td>0.1</td>
<td>0.2</td>
<td></td>
<td>15 min.</td>
<td>2.3</td>
<td>1.5</td>
</tr>
<tr>
<td>30 min.</td>
<td>0.2</td>
<td>0.3</td>
<td></td>
<td>30 min.</td>
<td>1.7</td>
<td>1.1</td>
</tr>
<tr>
<td>120 min.</td>
<td>0.5</td>
<td>1.0</td>
<td>0.5</td>
<td>60 min.</td>
<td>1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>4 hr.</td>
<td>0.8</td>
<td>2.4</td>
<td>10.6</td>
<td>120 min.</td>
<td>0.7</td>
<td>16.5</td>
</tr>
<tr>
<td>6 hr.</td>
<td>0.4</td>
<td>4.5</td>
<td>13.4</td>
<td>4 hr.</td>
<td>0.5</td>
<td>21.7</td>
</tr>
<tr>
<td>24 hr.</td>
<td>0.1</td>
<td>8.8</td>
<td>19.4</td>
<td>8 hr.</td>
<td>0.3</td>
<td>28.4</td>
</tr>
<tr>
<td>48 hr.</td>
<td>10.7</td>
<td>0.0</td>
<td>13.3</td>
<td>24 hr.</td>
<td>0.1</td>
<td>36.4</td>
</tr>
<tr>
<td>72 hr.</td>
<td>0.0</td>
<td>11.3</td>
<td>16.4</td>
<td>48 hr.</td>
<td>0.1</td>
<td>41.1</td>
</tr>
<tr>
<td>96 hr.</td>
<td>0.0</td>
<td>11.8</td>
<td>16.9</td>
<td>72 hr.</td>
<td>0.1</td>
<td>43.5</td>
</tr>
<tr>
<td>120 hr.</td>
<td>12.0</td>
<td>0.0</td>
<td>17.6</td>
<td>96 hr.</td>
<td>0.1</td>
<td>45.1</td>
</tr>
<tr>
<td>144 hr.</td>
<td>12.2</td>
<td>21.1</td>
<td>17.9</td>
<td>120 hr.</td>
<td>0.1</td>
<td>46.4</td>
</tr>
<tr>
<td><strong>Daily excretion of activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 days</td>
<td>0.09%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>71 days</td>
<td>0.07%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 days</td>
<td>0.02%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>73 days</td>
<td>0.10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
per sample were collected. These fractions were counted either directly, or following combustions, on a Packard Tri-Carb scintillation counter, model 314 EX, using the same composition of absorption and scintillation mixture in both cases (11). The fractions containing radioactivity were lyophilized and checked with thin-layer chromatography for their identity and compared with the original compound. The system used was chloroform:methanol (1:1), the adsorbent was Al₂O₃ as described earlier (14). Also, continuous thin-layer chromatography, as described by Brenner and Niederwieser (1), proved very useful; for this, Al₂O₃ was used as adsorbent, and n-butanol saturated with 15% NH₄OH, or n-butanol saturated with H₂O, was used as solvent. The plates were developed during 30–45 hr.

An ultraviolet lamp was used for the identification of the spots in a few cases; in most cases, however, Dragendorff’s reagent was employed. A strip scanner, model RSC-302, by Atomic Accessories, was used for radioactive spots.

For several determinations of C¹⁴-NSC-57155, the spots identified with Dragendorff’s reagent were scraped off the thin-layer plate and counted in the Packard Tri-Carb liquid scintillation counter in the same solvent mixture as used for the combustion analysis.

RESULTS

STUDIES WITH C¹⁴-NSC-38280 FOLLOWING ADMINISTRATION BY CONTINUOUS I.V. INFUSION

Blood.—A comparison of the values found in the 3 patients after I.V. infusion showed a good correlation in the time/blood level concentration (Table 1). Since the dosage was low and the administration slow, the amount of radioactivity found in the blood was also low. Furthermore, the concentration decreased rapidly, the half life of the drug being about 2 hr. after the end of infusion. This is 4 times the half life found in mice after a single I.V. injection (13).

In a more specific evaluation of the same series (patient 3), the relation of time to distribution of the radioactivity of the corresponding WBC, RBC, and plasma in 1.0 ml of whole blood was studied (Table 2). Q indicates the quotient of activity in plasma divided by the activity in the RBC/ml of blood. It shows a rapid drop from 12.5 to 0.6, probably revealing a dilution of the plasma radioactivity into extracellular water or other intracellular spaces. The low activity of the WBC does not mean that there is much less substance in or on the WBC, as compared with the RBC, but only indicates the probable statistical distribution of the activity over all blood cells.

Urine.—Table 1 gives the additive percentage of the administered activity excreted in various urine portions. The average excretion of activity in urine during the first 24 hr. was 13.8% and is comparable to the value found in rat experiments (21.2%) (13). Half of this amount was excreted during the first 4–8 hr. The average excretion of 3 144-hr. collections was 17.1% of the administered activity.

Spinal fluid.—One determination of spinal fluid, 24 hr. after the start of infusion, showed only 12 c.p.m./ml above background and can, therefore, be ignored. This result is in good correlation with the findings in the mouse brain (13), indicating that there is only insignificant or no passing of the substance through the blood/spinal fluid barrier.

STUDIES WITH C¹⁴-NSC-38280 FOLLOWING P.O. ADMINISTRATION

Blood.—All results were close to the blank values. The highest activity 27 hr. after administration of the drug was as little as 0.02 µg/ml. This is the 1st indication that the absorption was extremely low, but even such a small amount could be due to the absorption of a metabolite or a fragment of the compound.*

Urine.—Results are shown in Table 3. In patient 4 the

* In enzymatic studies of gastrointestinal tracts and ascites cells of P515(8) and P388(25) leukemic mice (13), however, no indication was given of a lysis of the CO-NH linkage in NSC-38280.

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**TABLE 2**

<table>
<thead>
<tr>
<th>HR. AFTER START OF INFUSION</th>
<th>INFUSION OF SOLUTION APPLIED (ML)</th>
<th>C.P.M.</th>
<th>Q</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole blood</td>
<td>Suspension of</td>
<td>Plasma</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>180</td>
<td>512</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>360 (end)</td>
<td>941</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>—</td>
<td>438</td>
<td>123</td>
</tr>
<tr>
<td>7</td>
<td>—</td>
<td>268</td>
<td>97</td>
</tr>
<tr>
<td>24</td>
<td>—</td>
<td>58</td>
<td>41</td>
</tr>
<tr>
<td>48</td>
<td>—</td>
<td>38</td>
<td>13</td>
</tr>
<tr>
<td>72</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>96</td>
<td>—</td>
<td>8</td>
<td>—</td>
</tr>
</tbody>
</table>

**TABLE 3**

<table>
<thead>
<tr>
<th>TIME AFTER BEGINNING EXPERIMENT (HR.)</th>
<th>C.P.M./URINE SPECIMEN</th>
<th>% OF TOTAL</th>
<th>TIME AFTER BEGINNING EXPERIMENT (HR.</th>
<th>C.P.M./URINE SPECIMEN</th>
<th>% OF TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5,580</td>
<td>0.22%</td>
<td>0–23</td>
<td>170,400</td>
<td>0.46%</td>
</tr>
<tr>
<td>1</td>
<td>1,080</td>
<td>0.06%</td>
<td>0–23</td>
<td>170,400</td>
<td>0.46%</td>
</tr>
<tr>
<td>2</td>
<td>8,228</td>
<td>0.6%</td>
<td>0–23</td>
<td>170,400</td>
<td>0.46%</td>
</tr>
<tr>
<td>3</td>
<td>6,708</td>
<td>0.5%</td>
<td>0–23</td>
<td>170,400</td>
<td>0.46%</td>
</tr>
<tr>
<td>4</td>
<td>7,379</td>
<td>0.5%</td>
<td>0–23</td>
<td>170,400</td>
<td>0.46%</td>
</tr>
<tr>
<td>6</td>
<td>12,160</td>
<td>0.8%</td>
<td>0–23</td>
<td>170,400</td>
<td>0.46%</td>
</tr>
<tr>
<td>8</td>
<td>8,625</td>
<td>0.5%</td>
<td>0–23</td>
<td>170,400</td>
<td>0.46%</td>
</tr>
<tr>
<td>12</td>
<td>17,120</td>
<td>1.0%</td>
<td>0–23</td>
<td>170,400</td>
<td>0.46%</td>
</tr>
<tr>
<td>24</td>
<td>22,260</td>
<td>1.4%</td>
<td>0–23</td>
<td>170,400</td>
<td>0.46%</td>
</tr>
<tr>
<td>0–120</td>
<td>370,220</td>
<td>2.3%</td>
<td>0–120</td>
<td>370,220</td>
<td>2.0%</td>
</tr>
</tbody>
</table>
very low absorption seemed to have stopped completely after 5 days, whereas in patient 5 it must have continued after this time. Considering that the urinary excretion of the drug after I.V. administration is in the range of 9–19% of the administered dose (mean: 13.8%) within the first 24 hr., the 0.2 and 0.5%, respectively, within the same period following P.O. administration correspond to an absorption of 2.5% in both cases. This is close to the 2% found in the rat experiments (13). Here, too, the question remains whether the whole molecule or only part of it has been absorbed.

**Feces.**—Samples, taken from patient 4 25 hr. following P.O. administration of the drug, showed an excretion of 37% and, after 52 hr., a total of 90% of the administered activity. These findings also indicate very little absorption of the compound.

**Studies with C14-NSC-57155 Following Administration by I.V. Injection**

**Blood.**—Samples taken immediately following I.V. injection showed, as expected, the highest concentration: 2.3 and 1.5 µg/ml, respectively (Table 1). The decrease was somewhat more rapid than with NSC-38280, with a half life of approximately 45 min. After 24 hr. only 0.1 µg/ml of the administered activity could be found in patient 6 and nothing in patient 7, which compares favorably with the values found in the patients receiving NSC-38280 by I.V. infusion.

**Urine.**—After the injection of C14-NSC-57155, the excretion started relatively rapidly (Table 1). After 4 hr. approximately 22 and 26%, respectively, of the injected activity were found in the urines of patients 6 and 7; and after 24 hr. the values were 36 and 42%. Then the excretion slowed down considerably and, from the 4th day on, remained constant during the following 4 days, the average excretion being approximately 1.0%/day. Compared with NSC-38280, the excretion rate and quantity were tripled. The activity in the urine of patient 7 was checked 70–73 days following the injection. During this period, daily values of 0.09, 0.07, 0.02, and 0.1% of the total injected activity were found. An attempt was made to chromatograph these urines to determine whether the activity was due to NSC-57155. However, the activity was too low for a definite identification. If the suggestion is correct that most of the compound is excreted in the urine, then the extrapolated excretion time for this and perhaps other related compounds may be more than 400 days.

**Chromatographic Studies**

Normal urine samples of patient 7, before administration of the labeled compound, and samples of healthy adults, to which C14-NSC-57155 was added, showed the same pattern of radioactivity on column chromatography as urine samples of patient 7 after injection of the labeled compound (Chart 1). Furthermore, in all urine samples studied, collected 15 min. to 96 hr. after injection, only 1 peak of radioactivity was found. Thin-layer plates revealed the identity of the various fractions of the column chromatographies with those of all urine specimens of both patients, which were not chromatographed. However, when compared with pure NSC-57155, the urine samples were found to migrate more rapidly (Chart 2). This difference in Rf-values ranged widely, depending especially on the solvent system used and probably on room temperature and humidity.

In few instances, when large amounts of substance were applied to the starting points, we found 2 or even 3 spots migrating faster than the original NSC-57155 on our thin-layer plates with the usual staining technic. These were believed to be artifacts which also appeared in some experiments with pure NSC-57155.

The sickle-like shape of the spots reminds one of the spots obtained with the "Keilstreifentechnik" of Reindel.
CONTINUOUS THIN LAYER CHROMATOGRAPHY

Adsortent: Aluminoxyd Fluka D5
System: n-Butanol saturated with 15 % aqueous NH₄OH
Time exposed: 48 hours
Identification of the spots with Dragendorff’s reagents
1. Urine of pat 6 collected 30-60 min after injection: small amount applied.
2. Normal human urine + NSC 57155
3. Urine of pat 6 collected 30-60 min after injection: large amount applied.
4. Normal human urine + NSC 57155 (same as 2)
5. NSC 57155 (inactive substance)

CHART 2.—Comparison by continuous thin-layer chromatography of urine of patient 6, 30-60 min after injection of C¹⁴-NSC-57155, with normal urine to which NSC-57155 was added, and aqueous solution of NSC-57155.

and Hoppe (26) and Matthias (19) and can also be seen on thin-layer chromatograms of sugars in urine (27).

**Feces.**—Within 6 days, only 1.1 % of the administered activity appeared in the stool.

**Expired air.**—In the 2 samples of expired air, taken 15 min. and 2 hr., respectively, after injection of the compound, no radioactivity in the form of C¹⁴O₂ could be found. This negative finding confirmed the experiments with rats.

**DISCUSSION**

The results of this study have shown relatively low levels and a rapid fall of the concentration of both compounds in the blood. Although the 2 compounds are usually administered in higher doses than those used for our studies, it is probable that higher doses would show the same short half life. This may be one reason for the relative lack of antileukemic activity of these substances in generalized leukemia in humans, compared with their very good effects in some mouse ascites leukemias (4, 15, 33) in which, as reported previously (13), the I.P. and I.V. injected substance showed relatively high concentrations in the ascites fluid over a long period.

A study by Rogers et al. (28) on a patient who received NSC-38280 showed a rapid rise and a rapid fall to background level of drug equivalent within 24 hr. in whole blood. After a 2d dose there was a higher postinjection level and the background level was not reached within 2 days. Similar findings were obtained in plasma of another patient who received NSC-35843 (terephthalanilide 4',4'-di (2-imidazolin-2-yl)-dihydrochloride) by I.V. infusion.

The difference in the maximal concentrations of the 2 compounds in blood is probably due to the technic of administration (I.V. infusion of NSC-38280 over 4 hr. and I.V. injection of NSC-57155 over 15 min.). The half life of NSC-38280 was found to be longer in patients (2 hr.) than in mice (approximately 30 min.) (13).

Although the excretion of radioactivity in urine within 144 hr. after administration of C¹⁴-NSC-57155 (49.4 %, average of 2) was almost 3 times larger than that after administration of C¹⁴-NSC-38280 (17.1 %, average of 3), the former is still considered very slow. In our mouse studies, with repeated administration of C¹⁴-NSC-38280 a very significant accumulation of radioactivity was found, especially in kidneys and liver (13). The aim, therefore, is to find a compound, by altering the molecule in various ways, that is excreted faster and, above all, excreted completely. The differences in the physiologic disposition between NSC-57155 and NSC-38280 may represent at least a step in this direction.

Excretion via liver, bile, and feces was practically negligible in the case of 1 patient who had received NSC-57155 after 6 days only 1.1 % of the total activity had been eliminated in the stool. This was less than expected, since the rat experiments revealed an excretion in feces of 12.8 % of the injected activity of C¹⁴-NSC-57155 within 72 hr. (excretion in urine was 46.2 % within the same period). One spinal fluid sample of a patient who had received NSC-38280 showed no activity, confirming that the compound does not pass the blood/spinal fluid barrier. This is in accordance with the findings in mice (13).

The absorption of C¹⁴-NSC-38280 after P.O. administration is negligible and goes parallel to the findings in rats (13). This result is probably due to the strong polar, aromatic, and basic character of the compound.

Our interpretation of the chromatography studies is as follows: The structure of the NSC-57155 molecule is unchanged during its passage through the human body. However, a salt, complex, or conjugation product seems to form in the liver, kidneys, or urine. All our efforts, including chromatography on various ion exchangers, dialysis against water, and extraction with nonpolar solvents, failed to recover the original free base compound. This hypothesis has not been proven so far, since several

In a respiration experiment with a rat only negligible traces of the I.V. injected C¹⁴-NSC-57155 were found in the expired air collected over 26 hr. (unpublished data).

In a patient who—in 1 month—had received 119 mg of 4',4'' bis (2-imidazolin-2-yl-amino) terephthalanilide, dihydrochloride (NSC-53306) and 650 mg of NSC-57155 and then died, we found in the liver approximately 61 mg and in the kidneys approximately 7 mg of the remaining compounds 6 weeks after the last drug administration. To our surprise, abdominal fat revealed no remaining substance. The values found represent approximately 10% of the total amount administered.

Several spinal fluid samples of patients who had received unlabeled NSC-38280, but which were not included in this series, showed no positive color reaction for the presence of the compound. Three spinal fluid samples of a patient receiving NSC-53306 did not show any compound by our extraction procedure.

In a study by Rogers et al. (28) on a patient who received NSC-38280 showed no activity, confirming that the compound does not pass the blood/spinal fluid barrier. This is in accordance with the findings in mice (13).
attempts to find a complexing substance in the form of urea, bilirubin, or glucuronic acid failed. As only approximately 50% of the injected activity could be found and identified within 144 hr. after injection, the remaining 50% might be altered by a metabolic process and stored in liver, kidneys, and other tissues. Studies are in progress to find such alterations of the molecule of urea, bilirubin, or glucuronic acid.

The remaining 50% might be altered by a metabolic process and stored in liver, kidneys, and other tissues. Studies are in progress to find such alterations of the molecule of urea, bilirubin, or glucuronic acid. The molecule of urea, bilirubin, or glucuronic acid failed to be found and identified within 144 hr. after injection. Young for injection of the compound and collection of samples from 2 adult patients.

ACKNOWLEDGMENT

The authors are indebted to Dr. I. H. Krakoff and Dr. C. W. Young for injection of the compound and collection of samples from 2 adult patients.

REFERENCES

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