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# INTESTINAL ABSORPTION OF RADIOIODINE LABELLED HUMAN SERUM ALBUMIN, MONO-IODOTYROSINE AND DI-IODOTYROSINE FOLLOWING ABDOMINAL RADIATION THERAPY

by

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Research has been carried out for the last ten years on the intestinal damage induced by irradiation of the lower abdomen in the course of radiation therapy of tumours not involving the gastro-intestinal tract. This has included investigations of anatomic changes by conventional histologic methods, electron microscopy and histochemistry (DE GIULI et coll. 1965, DE DOMINICIS & GRECHI 1966).

Functional changes were investigated by determining the absorption of fatty acids, neutral fats, iron, vitamin $B_{12}$, xylose, glucose, sucrose, intestinal loss of macromolecules and biliary and pancreatic secretions (DE GIULI et coll. 1965, GIANNARDI et coll. 1965, DALLA PALMA et coll. 1965, DALLA PALMA 1968). Morphologic changes in the intestinal loops not included in the field of irradiation have also been described (DE DOMINICIS & GRECHI 1965). All our previous and present work has been done in patients without signs of anatomic or

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**Table 1**

*Results of previous investigations of intestinal absorption damage induced by abdominal irradiation*

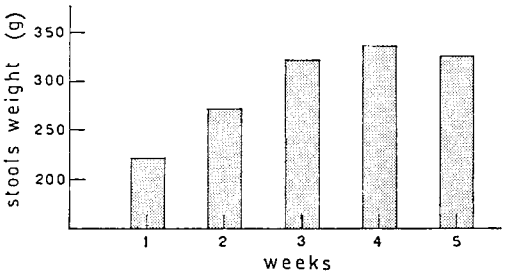
| Substance | Treatment | | | No. of patients |
|---|---|---|---|---|
| | Before | Halfway | End | |
| *Absorption (mean %)* | | | | |
| Oleic acid | 88.26 | 80.87 | 78.38 | 24 |
| Triolein | 89.04 | 69.93 | 64.25 | 21 |
| Iron | 39.11 | 10.94 | 28.19 | 18 |
| Vitamin $B_{12}$ | 51.10 | 33.00 | 36.00 | 20 |
| *Maximum blood level (mean %)* | | | | |
| Glucose | 55.40 | 41.60 | 37.40 | 50 |
| Sucrose | 61.70 | 39.10 | 36.90 | 22 |
| *Faecal loss (mean %)* | | | | |
| PVP | 0.52 | 0.77 | 1.10 | 14 |
| *Urinary excretion (mean g/5 hrs)* | | | | |
| D-Xylose | 6.30 | 4.30 | 4.20 | 28 |

functional conditions in the digestive tract before treatment. The tests were carried out at least twice, more often three times, in each individual patient, before, halfway through and at the end of treatment.

Table 1 gives the conclusive data obtained in previous work on the radiation-induced malabsorption of investigated substances. The variations in the weight of stools during treatment are indicated in the Figure.

*Material and Method.* Protein intestinal absorption in the present series was investigated in a group of female patients with tumours of the uterus admitted for radiation therapy after total hysterectomy and bilateral oophorectomy. The technical data of the treatment (Cobalt 60) have been reported in a previous paper (De Giuli et coll. 1965).

The early stage of the investigations was limited to an evaluation of the absorption of $^{131}I$ labelled human serum albumin (RISA); later, mono-iodotyrosine (MIT) and di-iodotyrosine (DIT) absorption were also followed. Each of these iodinated aminoacids was administered to two different groups of patients at the same time as albumin, using two radioactive isotopes of iodine, $^{131}I$ in the case of MIT and $^{125}I$ for labelling DIT. The RISA in the investigation was labelled on tyrosine either with $^{125}I$ or with $^{131}I$ depending on whether the aminoacid administered at the same time was labelled with $^{131}I$ (MIT) or with $^{125}I$ (DIT). All the tracers were provided by the Radiochemical Centre, Amersham, England. The extent of the spontaneous degradation of the labelled compounds was tested before use by paper chromatography.




Daily weight of stools (average values) in the five weeks during therapeutic treatment to the abdomen.

The patients were given twenty drops of Lugol solution three times a day during the three days before the test in order to prevent thyroid uptake. Fifty $\mu$Ci of each tracer were administered to the fasting patient together with a high protein diet consisting of 120 g of 'ricotta' (a type of cottage cheese) with a protein content of about 14 g. Food was withheld for at least three hours following the administration of the labelled dose.

During the following four days the stools were collected, the patients evacuating, carefully excluding urine, directly in one litre plastic containers. The stools were brought to constant volume with water and homogenized by means of an electric mixer to obtain uniform distribution of radioactivity before the latter was measured. The containers, in reproducible geometry, were placed in contact with a scintillator connected with a multichannel pulse analyser which allowed the discrimination of the photoelectric peaks of the two iodine isotopes employed. The excreted fraction was evaluated by comparison with a sample prepared at the same time as the dose and containing a known quantity of the same. The tests were carried out on each patient before, halfway through (2 500 to 3 000 R) and at the end (5 000 R) of the treatment.

MIT was chosen because its use would demonstrate any impairment of enzymatic hydrolysis since the albumin is labelled on tyrosine. DIT was selected because it might be indicative of the part of the absorption occurring by simple diffusion.

## Results

The results relating to the absorption of the three substances investigated are reported separately and then compared where both were administered. Table 2 gives the individual results as well as the condition of the abdomen during the period when the absorption test was being carried out. Three different types of reaction are represented schematically in Table 3, in which the number of patients with each type of reaction is indicated for the three substances. No explanation for the differences in the behaviour can be offered at this stage.

**Table 2**

*Absorption of RISA, MIT or DIT expressed as a percentage of the administered dose — The eight patients with initial absorption values of RISA below 94 per cent are indicated by**

| Case | RISA | | | MIT | | | DIT | | | Diarrhoea | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Before | Half-way | End | Before | Half-way | End | Before | Half-way | End | Halfway | End |
| 1 | 95.9 | 94.8 | 92.1 | | | | | | | + — — | + + — |
| 2 | 95.1 | 93.6 | 93.7 | | | | | | | + + — | + + + |
| 3 | 95.0 | 95.0 | 92.9 | | | | | | | + + — | + + — |
| 4 | 94.5 | 93.6 | 93.7 | | | | | | | + + + | + + + |
| 5 | 96.7 | 92.7 | 86.8 | | | | | | | + + — | + + — |
| 6 | 97.6 | 92.4 | 70.7 | | | | | | | + — — | + + + |
| 7 | 98.3 | 95.3 | 93.8 | | | | | | | + + — | + + — |
| 8 | 96.8 | 93.0 | 92.3 | | | | | | | + + + | + + — |
| 9 | 95.2 | 67.0 | 89.0 | | | | | | | — — — | — — — |
| 10 | 96.6 | 93.4 | 99.1 | | | | | | | + + — | + — — |
| 11 | 98.3 | 95.3 | 93.8 | | | | | | | + + — | + + — |
| 12 | 94.5 | 89.5 | 89.5 | | | | | | | + + — | + + — |
| 13 | 96.8 | 85.2 | 90.3 | | | | | | | — — — | — — — |
| 14 | 96.2 | 95.5 | 95.8 | 92.6 | 90.0 | 85.7 | | | | + — — | + + — |
| 15 | 96.6 | 83.2 | 93.3 | 82.8 | 78.7 | 90.9 | | | | — — — | — — — |
| 16 | 97.9 | 85.2 | 94.2 | 95.4 | 86.5 | 92.8 | | | | + + — | + + — |
| 17 | 94.0 | 94.4 | 90.9 | 93.0 | 70.2 | 94.7 | | | | + + — | — — — |
| 18 | 98.0 | 91.0 | 97.4 | 97.2 | 91.7 | 87.9 | | | | — — — | — — — |
| 19 | 94.4 | 91.3 | 91.7 | 95.3 | 85.1 | 80.9 | | | | + — — | — — — |
| 20 | 98.2 | 96.3 | 95.5 | 92.0 | 95.8 | 81.7 | | | | — — — | — — — |
| 21 | 99.6 | 97.8 | 91.2 | 98.5 | 97.4 | 90.3 | | | | — — — | — — — |
| 22 | 99.2 | 79.3 | 96.2 | 99.3 | 87.0 | 94.6 | | | | — — — | — — — |
| 23 | 94.4 | 92.2 | 98.5 | 92.1 | 92.4 | 98.2 | | | | — — — | + — — |
| 24 | 96.1 | 95.0 | 93.5 | 96.0 | 95.0 | 93.8 | | | | + + — | + — — |
| 25 | 96.3 | 87.5 | 93.9 | 93.7 | 90.8 | 94.1 | | | | — — — | — — — |
| 26 | 96.2 | 88.6 | 96.2 | 92.6 | 85.3 | 93.1 | | | | + — — | + — — |
| 27 | 94.9 | 88.2 | 92.2 | 94.2 | 93.1 | 88.0 | | | | — — — | — — — |
| 28 | 99.9 | 94.6 | 93.7 | 98.7 | 92.8 | 98.4 | | | | + + — | + — — |
| 29 | 99.0 | 96.3 | 90.0 | 99.0 | 92.4 | 98.0 | | | | — — — | — — — |
| 30 | 99.0 | 99.0 | 99.8 | 99.0 | 99.0 | 98.0 | | | | — — — | — — — |
| 31 | 97.7 | 97.4 | 98.1 | 95.0 | 95.5 | 94.0 | | | | — — — | — — — |
| 32 | 94.2 | 91.5 | 95.1 | 90.8 | 89.5 | 99.3 | | | | + + — | + + — |
| 33 | 99.0 | 91.2 | 97.8 | 97.8 | 94.3 | 92.0 | | | | + — — | — — — |
| 34 | 95.4 | 92.0 | 81.8 | | | | 87.5 | 82.1 | 56.7 | + + — | + — — |
| 35 | 95.3 | 88.0 | 78.3 | | | | 92.9 | 77.2 | 59.2 | + — — | + + — |
| 36 | 97.1 | 91.3 | 89.7 | | | | 95.0 | 75.9 | 62.2 | + + — | + — — |
| 37 | 95.6 | 77.4 | 75.8 | | | | 91.2 | 73.7 | 57.3 | + — — | + + — |
| 38 | 96.4 | 91.4 | 90.4 | | | | 96.3 | 76.6 | 73.7 | — — — | — — — |
| 39 | 97.5 | 87.4 | 88.8 | | | | 91.5 | 91.5 | 76.4 | + + + | + + — |

**Table 2** (*cont.*)

| Case | RISA | | | MIT | | | DIT | | | Diarrhoea | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Before | Half-way | End | Before | Half-way | End | Before | Half-way | End | Halfway | End |
| 40 | 96.5 | 89.5 | 97.9 | | | | 84.1 | 72.3 | 93.9 | + + — | + — — |
| 41 | 94.4 | 87.5 | 91.9 | | | | 94.2 | 76.8 | 78.8 | + + — | + + + |
| 42 | 96.3 | 86.7 | 91.7 | | | | 85.9 | 92.4 | 57.5 | + + + | + — — |
| 43* | 88.0 | 95.4 | 94.1 | 91.8 | 74.2 | 82.4 | | | | — — — | — — — |
| 44* | 91.3 | 91.3 | 93.4 | 95.3 | 85.3 | 93.5 | | | | + + + | + — — |
| 45* | 92.3 | 94.2 | 93.7 | 95.4 | 80.9 | 92.6 | | | | — — — | — — — |
| 46* | 92.6 | 90.0 | 94.3 | 92.7 | 91.0 | 90.3 | | | | + + — | + + — |
| 47* | 91.7 | 93.9 | 91.7 | | | | | | | + — — | + + — |
| 48* | 93.0 | 95.1 | 93.4 | | | | | | | — — — | — — — |
| 49* | 92.2 | 80.3 | 88.6 | | | | | | | + — — | + + — |
| 50* | 88.9 | 97.8 | 97.5 | | | | | | | + + + | + + — |

*RISA absorption* was investigated in 50 patients (Table 2). The evaluation however excludes a group of 8 subjects who, at the beginning of treatment, presented an absorption value under 94 per cent of the administered dose — a value generally given as the lower normal limit (LAVIK et coll. 1952, CHINN et coll. 1952, KIEKENS 1963). Table 4 indicates the average values in the tests carried out in the remaining 42 patients.

*MIT absorption.* The absorption values at the beginning of treatment of the present material were slightly lower than those of RISA (Table 1). It would appear that no normal MIT intestinal absorption values are given in the literature for the method followed. Twenty of the 24 patients in whom the MIT absorption was evaluated belonged to the group with normal RISA absorption values in the first test and 4 gave values below normal. All those investigated were included in the statistical evaluation. The average values obtained are presented in Table 5.

*DIT absorption.* This presented values more variable and, on the whole, lower than those for RISA and MIT in the present material before treatment. Again no normal absorption values appear in the literature for this aminoacid.

Nine subjects, all included in the group having RISA initial absorption values within normal limits, were investigated (Table 6).

*RISA — MIT association.* RISA and MIT absorption was investigated at the same time in 24 patients; the average values obtained with these two substances in this group are given in Table 7.

*RISA — DIT association.* The absorption of RISA and DIT was investigated at the same time in 9 patients. Table 8 details the average results obtained for the two substances in this group.

**Table 3**

*The types (A, B and C, respectively) of reaction (schematic) and the number of patients for the three substances with each reaction*

| Before | Halfway | End | RISA | MIT | DIT |
|---|---|---|---|---|---|
|  |  |  | 17 | 8 | 6 |
|  |  |  | 21 | 11 | 3 |
|  |  |  | 4 | 5 | 0 |

## Discussion

The most important part of the ingested protein is absorbed in the form of aminoacids although it is known that under normal conditions a small quantity of intact proteins and polypeptides is absorbed. Depending on the steric configuration of the molecule, the absorption of aminoacids may occur by active transport or by simple diffusion and take place in elective areas along the small intestine. Tyrosine and its halogenated derivatives are among aminoacids whose absorption mechanisms has been determined. These have been used in this investigation.

NATHANS et coll. (1960) and HUANG (1961) have demonstrated with hamster intestinal loops that only L-tyrosine and its monohalogenated derivatives are absorbed against concentration gradients, while the derivatives di-substituted in 3 and 5 with Br and I, go through the intestinal wall only by means of passive diffusion.

The introduction of the two atoms of halogen induces ionization in the phenolic group and prevents active transport by abolishing the affinity for the carrier.

Among the proteins labelled with radioactive tracers, employed in investigation of intestinal absorption, the most favoured is $^{131}I$ serum albumin (RISA), which was introduced by LAVIK et coll. (1952) and by CHINN et coll. (1952). The principal advantage of $^{131}I$ albumin consists in favourable counting conditions when compared with the other proteins used in investigations of this kind, labelled by means of beta emitting isotopes as $^{3}H$ and $^{14}C$ and stable isotopes as $^{15}N$ (JEEJEEBHOY et coll. 1964, CRANE & NEUBERGER 1960). A further

**Table 4**

*RISA absorption. Average percentage variations to initial value ($X_0$) of values ($X_i$) observed halfway and at the end of treatment in fourth column*

| Treatment | No. of patients | Absorption (mean % ± SE) | $\left(\overline{\frac{X_i - X_0}{X_0}}\right)$ % ± SE | Significance (t-test) |
|---|---|---|---|---|
| Before | 42 | 96.55 ± 0.259 | | |
| Halfway | 42 | 90.65 ± 0.924 | −6.24 ± 0.93 | $<0.001$ |
| End | 42 | 91.88 ± 0.923 | −4.86 ± 0.95 | $< 0.01$ |
| | | | | $> 0.001$ |

**Table 5**

*MIT absorption. Average percentage variations to initial value ($X_0$) of values ($X_i$) observed halfway and at the end of treatment in fourth column*

| Treatment | No. of patients | Absorption (mean % ± SE) | $\left(\overline{\frac{X_i - X_0}{X_0}}\right)$ % ± SE | Significance (t-test) |
|---|---|---|---|---|
| Before | 24 | 94.59 ± 0.742 | | |
| Halfway | 24 | 88.91 ± 1.368 | −5.99 ± 1.38 | $< 0.01$ |
| End | 24 | 91.88 ± 1.079 | −2.80 ± 1.24 | $< 0.02$ |

**Table 6**

*DIT absorption. Average percentage variations to initial value ($X_0$) of values ($X_i$) observed halfway and at the end of treatment in fourth column*

| Treatment | No. of patients | Absorption (mean % ± SE) | $\left(\overline{\frac{X_i - X_0}{X_0}}\right)$ % ± SE | Significance (t-test) |
|---|---|---|---|---|
| Before | 9 | 91.98 ± 1.279 | | |
| Halfway | 9 | 79.29 ± 2.162 | −13.08 ± 2.68 | $< 0.01$ |
| End | 9 | 72.29 ± 4.732 | −20.57 ± 5.86 | $< 0.01$ |

advantage of RISA is the slight significance of the recycling phenomena of the tracer; the $^{131}I$, which is released by hydrolysis from the labelled molecules absorbed, is in fact almost totally eliminated with the urine owing to the thyroid block induced by the Lugol solution administered on days preceding the test. The quantity of isotope which can be re-excreted into the intestine is therefore such that it does not affect the measurement of the tracer that has not actually been absorbed.

**Table 7**

*RISA and MIT association*

| Treatment | Substance | Absorption (mean % ±SE) | $\left(\frac{X_i - X_1}{X_1}\right)$ % ±SE |
|---|---|---|---|
| Before | RISA | 96.04±0.611 | |
| | MIT | 94.59±0.742 | |
| Halfway | RISA | 91.93±0.986 | —4.17±1.20 |
| | MIT | 88.91±1.468 | —5.99±1.38 |
| End | RISA | 94.60±0.517 | —1.42±0.75 |
| | MIT | 91.88±1.079 | —2.80±1.24 |

**Table 8**

*RISA and DIT association*

| Treatment | Substance | Absorption (mean % ±SE) | $\left(\frac{X_i - X_1}{X_1}\right)$ % ±SE |
|---|---|---|---|
| Before | RISA | 96.05±0.325 | |
| | DIT | 91.98±1.279 | |
| Halfway | RISA | 87.91±1.467 | — 8.47±1.50 |
| | DIT | 79.29±2.162 | —13.08±2.68 |
| End | RISA | 87.35±2.400 | — 9.07±2.41 |
| | DIT | 72.29±4.732 | —20.57±5.86 |

On the other hand the aminoacids in the proteins labelled with isotopes of atoms normally present in them, such as $^{3}H$ and $^{14}C$, once they have been absorbed are re-utilized for the synthesis of new molecules which are partly re-excreted into the intestinal lumen. Some authors (JUNQUEIRA et coll. 1955, HANSSON 1959) have in fact demonstrated the presence of labelled pancreatic enzymes as early as 50 to 60 minutes after the intravenous administration of aminoacids labelled with $^{14}C$.

The main argument against the use of substances labelled with $^{131}I$ is the likelihood of release of radioactive iodine before absorption. Several authors have reported deiodinization values varying between 2 and 15 per cent of total radioactivity (LAVIK et coll. 1952, KIEKENS 1963, SHINGLETON et coll. 1955, FREEARK et coll. 1957).

The main conditions causing impairment in protein absorption are the following: (1) insufficiency of the enzymes that perform the hydrolysis of proteins and polypeptides, (2) decrease in the time of contact between the intestinal

content and the surface of the mucosa, and (3) destruction or atrophy of the intestinal mucosa.

Numerous authors who have investigated the pathologic states in which such conditions occur (KIEKENS 1963, LAVIK et coll. 1952, CHINN et coll. 1959, HOSAIN & BASU 1960, ALTHAUSEN & UYEYAMA 1954) have pointed out that even in the most serious situations the impairment of protein absorption is generally less significant than that for the other substances investigated at the same time.

Only experimental investigations have been carried out on radiation damage of protein intestinal absorption. BENNETT et coll. (1951) and KISELEY & OKULOV (1962) demonstrated in irradiated animals after the administration of labelled proteins, haematic radioactivity curves less steep than in control animals and ascribed this to a delay in the emptying of the stomach. They also tried to evaluate the possibility of diffusion of intact proteins or of high molecular weight polypeptides through the intestinal wall altered by radiation, however, no positive results were obtained.

Evaluation of the present results indicates that, in most of the patients investigated, therapeutic irradiation of the pelvis impaired the intestinal absorption of proteins. The damage was already evident halfway through the treatment (2 500 to 3 000 R), as was observed with other substances previously investigated. Generally those patients who halfway through treatment presented no evident impairment had none at the end.

Ninety per cent of the patients investigated had altered absorption halfway through the treatment; at the end some presented further impairment, others an improvement (reactions A and B of Table 3). It should be noted that halfway through the treatment the impairment was significantly different in these two groups of patients; the damage in fact was more serious in those patients with improvement at the end of treatment and less marked in those with further impairment.

No definite relationship was evident between the frequency of stools and the degree of malabsorption. In fact some patients had regular motions or even constipation with altered absorption; less frequently absorption was normal in patients with diarrhoea.

MIT and RISA produced an equivalent degree of impairment while DIT had a different effect. In the group of patients given both MIT and RISA, analysis disclosed that the two substances sometimes produced different reactions. The most frequent observation, for which no satisfactory explanation is at present forthcoming, was of more severe impairment arising from MIT particularly at the end of treatment. The impairment occasioned by DIT was more marked than by the other substances. The severity of the damage produced in all the

9 patients investigated was much greater with DIT either halfway through or at the end of treatment. As regards the effect in individual patients it should be noted that in none of them was no impairment of DIT absorption evident in both tests, while only in 3 patients did the absorption return to normal at the end of treatment.

These data seem to suggest that the prevailing damage caused by irradiation in the intestinal absorption affects the mechanism of parietal transit while the hydrolytic processes occur to a normal degree. This is probably dependent on the high concentration of proteolytic enzymes in the intestine during the passage of food and which is markedly in excess of physiologic needs.

Furthermore, investigations carried out by DALLA PALMA et coll. (1965) on the alteration of pancreatic and biliary secretions, demonstrated that the activity of the pancreatic enzymes never decreased so grossly as to suggest a possible impairment of the digestion of proteins taken with food.

As regards RISA and MIT the damage proved less significant than that occurring with other substances previously investigated, as can be seen by comparison of the present data with those in Table 1 relating to the previous research.

The present work has contributed further information concerning the state of malabsorption induced by abdominal irradiation and confirms the results already reported.

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## SUMMARY

Changes in the intestinal absorption of RISA, MIT and DIT in patients undergoing telecobalt therapy through abdominal fields were investigated. These substances, labelled with $^{131}I$ and $^{125}I$, were administered by mouth before, halfway through and at the end of treatment and the faecal activity was measured. An impairment of intestinal absorption of all three compounds occurred although to a lesser degree than in those previously investigated.

## ZUSAMMENFASSUNG

Es wurden die Änderungen der Absorption des Darmes für RISA, MIT und DIT bei Patienten, die bei der Telecobalt-Therapie mit abdominalen Feldern bestrahlt wurden, untersucht. Diese mit $^{131}I$ und $^{125}I$ gezeichneten Substanzen wurden per os vor, halbwegs und am Ende der Therapie verabfolgt und die Aktivität der Fäkalien gemessen. Eine Störung der intestinalen Absorption für alle drei Substanzen war, wenn auch in geringerem Umfang als bei früher untersuchten Substanzen, nachweisbar.

## RÉSUMÉ

Les auteurs ont étudié les modifications de l'absorption intestinale de RISA, MIT et DIT chez des sujets soumis à une télécobalt-thérapie par des champs abdominaux. Ces substances marquées avec $^{131}I$ et $^{125}I$, ont été administrées par voie orale avant, au milieu, et à la fin du traitement et l'activité fécale a été mesurée. L'absorption intestinale de ces trois substances est diminuée, cependant à un moindre degré que pour les substances étudiées précédemment.

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