

led to a request for the immediate preparation of such a solution. It was pointed out that if a base solution of 5% glucose were taken, the quarter-strength saline would easily be obtained by injecting into the glucose the requisite volume of sodium chloride concentrate. The calculation is as follows:

1 litre of "normal" saline contains 154 mEq of NaCl. 1 litre quarter "normal" would therefore contain approximately 38 mEq. Since the concentrate contains 5 mEq/ml., 38 mEq would be obtained by injecting $38/5=7.6$ ml. into a litre of 5% glucose (neglecting the small addition in volume). Had potassium also been required it would have been simple to make this further addition to the base solution.

The system has been accepted readily, usually with appreciation. It has greatly diminished the variety of special solutions which the pharmacy department is required to prepare and store, and seems to have improved the standard of treatment, because replacement is more thoughtfully planned and adjusted to the patients' needs rather than being adjusted to the type of solution which happens to be available. Each unit using infusion fluids is provided with a list of the solutions available, a brief explanation of the system, and a wall chart showing the colour code of the labels.

Summary

A system of intravenous fluids is described whereby the number of stock solutions is limited yet provides complete flexibility in the selection of concentration and amount to be administered. It simplifies calculation of the quantities of solute required for each patient.

Preliminary Communications

Carcinoid Syndrome: Alleviation of Diarrhoea and Flushing with "Deseril" and Ro 5-1025

Unfortunately the medical treatment of the carcinoid syndrome has almost always been ineffective. Therapy has been based on the assumption that the presenting clinical symptoms result from release of serotonin into the blood-stream. This concept, however, seems to represent an oversimplification, as Peart *et al.* (1961) have recently stated. Other substances besides 5-hydroxytryptamine are probably formed in excess in patients suffering from the carcinoid syndrome; these account, at least in part, for some of the symptoms. Although there are reports of improvement with various substances acting as serotonin antagonists in the literature no drug is known at the present time to be consistently beneficial.

The two most disturbing symptoms for the carcinoid patient are the diarrhoea and the flushes. We report below the effect in a patient with the carcinoid syndrome of 1-methyl-D-lysergic acid butanolamide tartrate (UML 491; "deseril") (Fanchamps *et al.*, 1960) and of 1-[p-dimethylamino-benzyl]-2[5-methyl-3-isoxazolyl-carbonyl]-hydrazine (Ro 5-1025, Hoffmann-La Roche).

CASE HISTORY

A 58-year-old man had suffered from shortness of breath and diarrhoea for five years. In 1958 he began to have facial flushing attacks; two years later they were of daily occurrence. In 1959 diarrhoea became resistant to the usual therapy. The 24-hour urinary output of 5-hydroxyindole

acetic acid varied between 143 and 674 mg. (normal upper limit 10 mg.). Radiological investigations failed to reveal the site of the primary neoplasm, but the liver was enlarged clinically. At necropsy in September, 1961, three small carcinoid tumours were discovered in the upper part of the ileum, with a secondary deposit in a mesenteric lymph node and two large metastases in the liver. The primary tumour contained 870 µg. of serotonin per g. of wet weight and the liver metastases 3.5–15 µg./g. (normal liver tissue up to 1 µg./g.).

In December, 1960, when deseril was given orally up to 6 mg./day, watery bowel movements stopped and were reduced to one formed movement daily. Diarrhoea returned when the drug was stopped, but it was controlled again when treatment was restarted (see Table). However, the flushes were not influenced by this therapy. The addition of Ro 5-1025 orally up to 75 mg./day decreased and shortened the duration of the very intense and annoying

Effect of Treatment

| Dates | No. of Stools f=Formed | No. of Flushes | UML 491 (mg.) | Ro 5-1025 (mg.) |
|------------------|---------------------------|-------------------|------------------|--------------------|
| 1960: December 6 | 4 | 7 | — | — |
| " 7 | 4 | 6 | — | — |
| " 8 | 3 | 5 | — | — |
| " 9 | 4 | 6 | — | — |
| " 10 | 3 | 4 | — | — |
| " 11 | 2 | 5 | — | — |
| " 12 | 3 | 4 | 1.5 | — |
| " 13 | 1 f | 5 | 2.0 | — |
| " 14 | 3 f | 4 | 2.5 | — |
| " 15 | 1 f | 6 | 3.0 | — |
| " 16 | 1 f | 7 | 4.0 | — |
| " 17–30 | 1–2 f | 4–7 | 6.0 | — |
| 1961: January 20 | 1 f | 4 | 4.0 | — |
| " 21 | 1 f | 3 | 4.0 | — |
| " 22 | 1 f | 0 | 6.0 | 20 |
| " 23 | 0 | 0 | 6.0 | 30 |
| " 24 | 1 f | 2 | 5.0 | 30 |
| " 25 | 1 f | 0 | 5.0 | 40 |
| " 26 | 2 f | 3 | 1.0 | 40 |
| " 27 | 3 | 2 | — | 50 |
| " 28 | 2 | 2 | 6.0 | 60 |
| " 29 | 1 f | 1 | 6.0 | 60 |
| " 30 | 1 f | 1 | 5.0 | 95 |
| " 31 | 1 f | 0 | 4.0 | 75 |
| February 1 | 2 | 2 | — | — |
| " 2 | 4 | 3 | — | — |
| " 3 | 4 | 4 | — | — |
| " 4 | 6 | 5 | — | — |
| March .. | 1 f | 1–2 | 3–4 | 75 |
| April .. | 1 f | 0–1–2 | 3 | 75 |
| May .. | 1–2 f | 5–7 | 3 | — |
| June .. | 1–2 f | 2–3 | 3 | 75 |
| July .. | 1–2 f | 2–3 | 3 | 70 |

flushes. When Ro 5-1025 was stopped flushing recurred immediately. With the combination of the two drugs the patient was relatively comfortable and was able to work half a day for a period of several months, up to one month before his death, which was due to cardiovascular complications.

DISCUSSION

In this case the administration of deseril and Ro 5-1025 clearly alleviated the diarrhoea and the flushes, though we are unable to explain their action.

Peart and Robertson (1961) reported on the effect of deseril in three patients who responded favourably in regard to diarrhoea. In one patient large doses of deseril (36 mg. a day orally), given alone, had an inhibitory effect on the flushes of the severe type with marked dyspnoea. In a woman (born 1913) with the carcinoid disease whom we have had under our observation, we were able to stop instantaneously a similar violent flushing attack, accompanied by severe dyspnoea and nausea, by the intravenous application of deseril (0.5 mg.). Lanz (1960) has reported a case of carcinoid disease in which deseril relieved the diarrhoea but had no effect on the other features. Schneekloth *et al.* (1959) stated that little or no benefit was seen.

The action of a new monoamine oxidase inhibitor Ro 5-1025, which at the same time inhibits amino-decarb-

oxylase, seems of particular interest and has to our knowledge not yet been tested in patients with the carcinoid syndrome. A definite reduction of the number of flushes and their duration in combination with deseril was observed in our patient. No hypotension or other adverse side-effects occurred with the two drugs.

Another substance, alpha-methyl-3-4-dehydroxy-D-1-phenylalanine (M.K. 351, Nr. C-2294, Merck Sharp and Dohme, Rahway, N.J.), has shown definite suppression of the flushes in our patient without affecting the diarrhoea (Dubach and Blumberg, 1961; Collini, 1961). However, this latter serotonin antagonist caused alarming side-effects in the psychical behaviour of the patient, necessitating discontinuance of the drug.

SUMMARY

Two serotonin antagonists, 1-methyl-D-lysergic acid butanolamide tartrate (UML 491; deseril) and 1-[p-dimethylamino-benzyl]-2[5-methyl-3-isoxazolylcarbonyl]-hydrazine (Ro 5-1025), were given by mouth to a patient with the carcinoid syndrome. The former drug reduced or stopped the diarrhoea; the latter, when given together with deseril, reduced the flushes from four to six to one to two a day. These effects were maintained over a period of several months to the benefit of the patient, who was able to continue to work up to one month before his death. No ill-effects of the two drugs were found.

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Medical Memoranda

Bilateral Phaeochromocytoma associated with Carcinoma of the Thyroid

Reports indicate that these two rare conditions coexist more often than might be expected by chance alone. This brief history of a further case is therefore of interest.

CASE REPORT

A single woman aged 29 was sent to hospital on August 7, 1960, as an emergency case by her general practitioner with a provisional diagnosis of "meningitis." She complained of the recent onset of episodes of severe frontal headaches and intermittent attacks of sharp pain in the neck. These attacks were associated with a sensation of "pins-and-needles" in the hands, and they lasted on each occasion for a few minutes. At the time of admission they had become increasingly frequent and were occurring about every half-hour. She also complained of a choking sensation, "as if something was stuck in my throat."

Three months prior to admission she had had pain in her left leg, and this was attributed to protrusion of the lumbar disk. Laminectomy had been performed at another hospital after full radiological examination. It is of interest to note in retrospect that at this time her blood-pressure fluctuated between 170/140 and 120/80. There was then no radiological evidence of metastases.

On admission her pulse was 100 and regular and blood-pressure 145/120. The fundi showed bilateral early papilloedema. The thyroid gland was enlarged and nodular, its consistency being firm. No other clinical abnormality was detected. A clean specimen of urine showed heavy glycosuria, albuminuria, and a small number of red cells and leucocytes. There were also a few granular, cellular, and hyaline casts. Blood chemistry, apart from showing elevated blood sugar and blood urea, was normal. X-ray examination of the chest could not be undertaken, as the least movement of the patient caused elevation of her blood-pressure to dangerous levels.

On the day after admission an "attack" was observed. The patient perspired very heavily and complained of severe frontal headache and agonizing pain in the back of the neck. Her extremities were cold and mottled in livid patterns. The pupils were widely dilated. The pulse rate was 128 and blood-pressure 210/150. A provisional diagnosis of hypertension due to phaeochromocytoma was made.

After this episode her blood-pressure was recorded every two hours. It fluctuated widely, the highest being 240/160 and the lowest 120/60. Her symptoms were so distressing that it was necessary to reduce the blood-pressure by hypotensive and sedative drugs. It was ultimately controlled at 170-180/110-100 approximately by pentolinium tartrate 10 mg. subcutaneously four-hourly, piperoxan 5 mg. subcutaneously 12-hourly, and chlorpromazine 50 mg. intramuscularly four-hourly. Further stabilization was achieved by raising the head or the foot of the bed.

A 24-hour specimen of urine showed a large excess of catechol amines. As the condition was deteriorating, urgent surgical treatment was advocated even before the result of the above investigation was known.

On August 13 a laparotomy was performed by Mr. Herbert Smith. Soft smooth suprarenal swellings about 2 in. (5 cm.) in diameter were palpated on each side. There were multiple hard nodules in the liver. Macroscopically they were typical of secondary metastases from carcinoma. In view of this a biopsy from one of the nodules in the liver was taken and the abdomen closed. The patient's condition continued to deteriorate, and she died on August 14, seven days after admission.

Post-mortem Examination.—The salient facts were slight hypertrophy of the left ventricle, widespread neoplastic deposits throughout the body except the brain, with a large nodule in the thyroid. There were bilateral suprarenal tumours, each about 3 by 2 in. (7.5 by 5 cm.) and cystic, containing clear fluid. Histological examination of post-mortem material and of the liver biopsy taken at operation showed a moderately differentiated adenocarcinoma of the thyroid gland with numerous metastases. The suprarenal tumours were phaeochromocytomata and showed no evidence of malignancy.

DISCUSSION

In recent years several reports have appeared of the association of these two extremely rare conditions.

In a review of 53 cases from the literature Eisenberg and Wallerstein (1932) brought to light a number of reports of single cases in which phaeochromocytoma has been associated with neoplasms in various organs, including one in which it was associated with carcinoma of the thyroid. It would appear, however, from subsequent reports that the only significant association is that with carcinoma of the thyroid. In other cases carcinoma of the thyroid has appeared months or even