has six secondary deposits, the right has eight). The liver is enormously enlarged to 8,010 g. by secondary deposits up to 7 cm. in diameter, most of which show extensive yellow foci of necrosis. An isolated secondary deposit is present in the twelfth thoracic body, and the first and second lumbar bodies are diffusely infiltrated by tumour. The breasts are readily separated from the surrounding tissues, and the left, without nipple, weighs 28 g.; section shows it to consist of firm fibrous tissue. The prostate is normal in size and appearance. The testes are not significantly reduced in size; they measure 4 by 2.5 by 2 cm. (with epididymis) and together weigh 28 g. The cut surfaces are brownish and atrophic.

The following organs show no obvious abnormalities: thyroid, pituitary, right adrenal, spleen (240 g.), brain (1,310 g.), heart (208 g.), and right kidney.

Histology.—This confirms the adrenal origin and carcinomatous nature of the tumour. Differentiation varies a great deal and nuclear irregularities are frequent, but even in the secondary deposits resemblances to adrenal cortical cells in nucleus and the lipid content of the cytoplasm are retained to a varying degree. Necrosis is everywhere a prominent feature, and in the sections studied half the tumour is necrotic. Whilst a fair degree of resemblance to adrenal cortical cells is present the picture nowhere approximates to that of the adrenal cortex or of a well-differentiated cortical adenoma, and in particular the normal relationship of cortical cells to sinusoids is nowhere evident. *Testes* show early atrophic changes with marked fibrous thickening of the walls of the tubules, diminution of the cellular content, and an increase of wear-and-tear pigment in the interstitial cells. *Breasts* show dilated ducts containing protein material and cells, and abundant glandular tissue, producing a picture not unlike that of a female breast.

Comment

Acquired feminism due to carcinoma of the adrenal cortex causes a well-defined syndrome of gynaecomastia, abdominal tumour, atrophy of the external genitalia, and loss of libido and potency. The condition is rapidly fatal, especially in the younger patients. Biochemically there are a moderate excess of urinary androgens and a gross excess of oestrogens. A most striking feature is the invariable presence of a palpable abdominal tumour.

The possibility that feminism might be due to hyperplasia of the adrenal cortex has been suggested by Broster and Vines (1933), who have clearly shown that virilism can be due to hyperplasia of the adrenal cortex as well as to carcinoma or adenoma. They consider that, similarly, feminism may be due to hyperplasia of the adrenal cortex. Roholm and Teilum (1942) also discuss this possibility.

In our clinic we are investigating cases of hypogonadism, with or without gynaecomastia, and are considering hyperplasia of the adrenals as a possible aetiological agent.

Summary

The condition of feminism is defined and discussed.

The eight reported cases due to carcinoma of the adrenal cortex are analysed in detail.

A clinical report and necropsy findings of a case of feminism due to carcinoma of the left adrenal are described.

Our thanks are due to Dr. J. G. Thomson, of the Department of Pathology, for the report on the necropsy and the histological findings, to Dr. Freda K. Herbert for the 17-ketosteroid investigations, and to Dr. S. Whately Davidson for the radiological reports.

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IDIOSYNCRASY TO *d*-TUBOCURARINE CHLORIDE

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Since first introducing pure *d*-tubocurarine chloride as an aid to anaesthesia it has been clear to us that patients show a marked variability in their reactions to average clinical doses of this substance. The following factors are known to influence the individual response.

Age.—As with most drugs, the administration of *d*-tubocurarine chloride must be made with caution in the extremes of age. Children up to the age of puberty tolerate the drug well provided that a dose-for-weight ratio (2 mg. per stone (6.35 kg.) body weight) is used. The aged, on the other hand, show a varying susceptibility, and some patients past the allotted span have required as much *d*-tubocurarine chloride as their lusty brethren in the prime of life.

Body Weight.—In so far as it bears a relation to muscle mass—e.g., in children—this is a useful guide to dosage, but in adults a maximum initial dose of 15 mg. should not be exceeded. It is, however, a general rule for the muscular well-developed patient to tolerate *d*-tubocurarine chloride well.

Physical Condition.—The dosage must be modified considerably in cachectic and feeble patients.

Drug Tolerance.—There is clinical evidence to show that patients who show a natural or acquired tolerance to the opiates and barbiturates tend to require a larger dose of *d*-tubocurarine chloride than normal.

Some authorities would modify the dose in the presence of certain anaesthetic agents, ether in particular. In our opinion it is preferable to reduce the amount of the toxic anaesthetic agent.

These, then, are the salient factors upon which the initial dosage of this drug is computed, but they do not account for all the variations. Minor variations in reaction on either side of normal are often seen, and the following two cases demonstrate very clearly that this variability may be of serious degree and consequence.

Case 1

The patient, a man aged 40, was admitted to hospital with an obstructive lesion of his main bronchus. He was losing weight and had a cough with repeated haemoptysis. Five days before the present examination a bronchoscope had been passed under local analgesia, but it was decided to repeat the examination and carry out a biopsy. The following sequence of events took place.

1 p.m.—Anaesthesia was induced with *d*-tubocurarine chloride, 15 mg., and thiopentone, 0.5 g., and respiratory arrest ensued. The lungs were inflated with oxygen, and bronchoscopy was performed. On bronchoscopy the picture was that of an inoperable carcinoma of the bronchus. Owing to the non-return of respiration the surgeon was asked not to take a biopsy. The examination was speedy and at no time was the patient deeply cyanosed, oxygen being insufflated through the side tube of the bronchoscope and artificial respiration performed whenever he went a little "off colour." At the close of the examination there was no sign of any respiration and the patient appeared to be more than usually relaxed and flaccid. An airway was introduced, a facepiece applied, and artificial respiration maintained by manual compression of the rebreathing bag of a closed-circuit anaesthetic machine.

After 30 Minutes.—"Prostigmin," 5 mg., and atropine, 1/50 gr. (1.3 mg.), were given intravenously. No effect of this was observed. The patient continued in apnoea.

After 60 Minutes.—The dose of prostigmin and atropine was repeated. Following this a little diaphragmatic respiration became evident. Within ten minutes, however, these slight respiratory efforts had ceased.

After 105 Minutes.—A further dose of prostigmin and atropine was administered with a very similar response, the respiration being temporarily stimulated but fading off after ten minutes.

After 165 Minutes.—The dose of prostigmin and atropine was repeated, and this time the slight diaphragmatic response was maintained. The general condition of the patient had remained excellent throughout, and the pulse and blood pressure were normal.

After 180 Minutes.—The patient was in good condition and was showing evidence of continued diaphragmatic respiration.

After 195 Minutes.—Blood-stained fluid was regurgitated from the stomach and some entered the air passages. Bronchoscopy was carried out without delay and as much fluid as possible was aspirated from the bronchial tree. The patient's blood pressure was 150/75 and his pulse rate 90 a minute, but from this time his condition began to deteriorate and for the first time cyanosis became a feature of the case, tending to increase despite vigorous artificial respiration with oxygen.

After 270 Minutes.—The pulse was of poor volume and the blood pressure had fallen. Ephedrine, $1\frac{1}{2}$ gr. (0.1 g.), was administered intravenously and slight improvement followed. The respiratory function was now practically in abeyance.

After 285 Minutes.—Nikethamide, 4 ml., was given intravenously, with a resultant transient improvement in the general condition. But circulatory failure was supervening.

After 300 Minutes.—The cyanosis had increased and the patient was now grey. Nikethamide, 4 ml., was repeated.

After 311 Minutes.—The pulse was imperceptible, and despite all efforts the patient died at 6.14 p.m., 314 minutes after the induction of anaesthesia.

Necropsy.—A very extensive carcinoma of the left main bronchus was found, and this rendered the whole of the left lung practically functionless. The right lung showed evidence of the aspiration of a large amount of blood-stained fluid which had undoubtedly reduced the aerating surface of this sole remaining lung below the minimum required for sustaining life. The stomach and intestines showed numerous small and recent punctate haemorrhages. These were not evident in the duodenum or in the large bowel. It was the blood from these which had been regurgitated from the stomach. Nothing else was found. There was no evidence of a persistent or enlarged thymus.

Remarks

This most severe case of hypersensitivity to *d*-tubocurarine chloride might not have been fatal had the possibility of regurgitation been anticipated and suitable precautions taken on the institution of artificial respiration. Before this accident the patient was apparently recovering and a fair degree of diaphragmatic respiration had returned. The necropsy was performed within three hours of death, and the haemorrhages of the gastro-intestinal tract were clearly of recent origin. The condition of the intestines bore a close resemblance to that discussed by Cole (1946) in his experiments performed on dogs to find a lethal dose of *d*-tubocurarine chloride. There was no suspicion or evidence of any myasthenic element in this case.

In view of this misfortune it was decided to give all patients a trial dose, namely, one-third of that estimated as necessary for the induction. That this was a wise precaution is amply confirmed by the sequence of events in Case 2.

Case 2

A woman aged 40 was found to be suffering from pulmonary tuberculosis in May, 1943. At no time had she complained of any symptom or shown any sign of myasthenia gravis, but she stated before operation that she had always reacted badly to drugs, especially to analgesics and opiates. Apart from the tuberculous disease of the right lung her condition was good and her blood picture normal. She was presented for a first-

stage thoracoplasty on the right side. After premedication with morphine, $\frac{1}{6}$ gr. (11 mg.), and atropine, $\frac{1}{150}$ gr. (0.43 mg.), one hour previously, *d*-tubocurarine chloride, 6 mg., was administered.

After 1 Minute.—The patient had become completely curarized and all respiration had ceased. A pharyngeal airway was introduced and the facepiece of a closed-circuit anaesthetic machine applied. The lungs were inflated with oxygen.

After 2 Minutes.—Thiopentone, 0.3 g., was injected and the patient was placed in the thoracoplasty position. The operation was started and the anaesthesia was maintained with a 50% mixture of oxygen and nitrous oxide.

After 45 Minutes.—Her respiratory efforts returned and the diaphragmatic contractions gradually increased in amplitude. The anaesthesia was perfectly satisfactory throughout the procedure, but there was more than the usual amount of haemorrhage.

After 130 Minutes.—The operation was completed. The respiratory excursion was now much improved, but it was still inadequate. Prostigmin, 5 mg., and atropine, $\frac{1}{50}$ gr. (1.3 mg.), were administered intravenously. This produced an immediate effect. All the reflexes were present when the patient left the table and she was fully conscious and co-operative ten minutes after arriving in the ward.

Further Progress.—The patient developed some basal consolidation accompanied by rusty sputum, but this cleared quickly and her convalescence was otherwise uneventful. On inquiry she stated that after the injection of *d*-tubocurarine chloride she felt "like a fish out of water"—as if she could not breathe. She could just remember the beginning of the injection of thiopentone.

Four weeks later she was presented for her second stage. The premedication was as before, and it was decided to follow the same regime as on the previous occasion in order to confirm the hypersensitivity. A test dose of 5 mg. of *d*-tubocurarine chloride was administered. The following sequence of events took place.

After 1 Minute.—There was complete ptosis of the eyelids and she was quite unable to raise them.

After 1 Minute 5 Seconds.—Her respirations were gasping and her pulse rate 130 a minute. She was showing signs of distress, and 0.3 g. of thiopentone was injected, the facepiece applied, and artificial respiration begun.

After 3 Minutes.—The facepiece was now accurately in position and the administration of a mixture of nitrous oxide and oxygen (25%) was started.

After 5 Minutes.—Manual full inflation of the lungs was met by a slight resistance at the end of the "stroke."

After 9½ Minutes.—There was some diaphragmatic flutter with slight arm movements; 0.2 g. of thiopentone was administered.

After 14 Minutes.—The respirations were regular but the tidal volume was small. The pulse rate was 80 a minute.

After 25 Minutes.—The respirations were still regular but small in volume and tending to be grunting. Pulse rate, 80 a minute.

After 43 Minutes.—The operation was terminating. Prostigmin, 3.5 mg., and atropine, $\frac{1}{50}$ gr. (1.3 mg.), were administered. An immediate effect was observed.

After 45 Minutes.—The patient was coughing and groaning. All her reflexes were present and she was practically conscious on return to bed. This time the post-operative course was uneventful. There was no urinary disturbance or melaena.

This patient had a third-stage thoracoplasty two weeks later. The dose of *d*-tubocurarine chloride was reduced to 2 mg., which again produced complete ptosis and respiratory arrest, which this time lasted for five minutes.

Remarks

The hypersensitivity to *d*-tubocurarine chloride shown by this patient on the occasion of her first operation was confirmed and placed beyond all possibility of reasonable doubt at the second and third operations. The difference between the dosage (1 mg.) accounted for the slightly less

severe reaction on the second occasion. It is interesting to speculate what would have happened if a preliminary small dose had not been administered.

Neither of these cases gave any history or symptom suggestive of myasthenia gravis, and the second has since been examined most carefully without disclosing any sign of this disease.

Discussion

For reasons which have been repeatedly stressed (Gray, 1947) we consider that *d*-tubocurarine chloride should be given before the induction of anaesthesia, and these two cases further urge the importance of this observation. But it is clear that the primary administration of this drug, whether at induction or during the course of an operation, should always be preceded by a trial dose not exceeding 5 mg. for the healthy adult. Its effects should be observed for at least two minutes before proceeding with the further administration. In the conscious patient a "normal" reaction to the trial dose is evidenced by a sensation of lassitude and fatigue and difficulty in keeping the eyes open; very rarely there may be a slight and transient diplopia.

Any ptosis that occurs should still be under voluntary control. If it is not, or if there are other signs of a more than usually severe reaction—e.g., persistent diplopia, dysarthria, or dysphagia—any subsequent dose should be reduced significantly. It does not need to be emphasized that if there is respiratory embarrassment after this small dose (Case ?) further administration should be abandoned.

Summary

The factors controlling the dosage of *d*-tubocurarine chloride are reviewed and two cases of extreme hypersensitivity are described; the advisability of the preliminary administration of a trial dose is stressed.

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Medical Memoranda

Perforation of the Posterior Fornix and Pouch of Douglas during Coitus

The following case is presented because of the rarity of this type of injury.

CASE HISTORY

The patient, a woman aged 57, had had eight children, the eldest being 37 and the youngest 15. She had travelled to the hospital by bus, and was seen at the receiving room. The history was that whilst having intercourse about one hour previously she experienced a sharp pain in the vagina and had since been bleeding slightly per vaginam. At the same time she felt a dull ache in the lower abdomen and this had persisted. Since the birth of her last child she had not menstruated. Intercourse had last been indulged in about twelve months previously.

On inspection the patient was pale and apprehensive but was not shocked. The pulse was 86, temperature 97.4° F. (36.3° C.), respirations 18, and blood pressure 110/80. The lower abdomen was resistant but not rigid. There was some tenderness over the hypogastrium. Vaginal examination revealed that there was a transverse tear in the posterior fornix about 1½ in. (3.75 cm.) in length, and a loop of intestine was felt to be lying in the wound. There was a trickle of blood from the vagina. She was placed in the left lateral position and a Sims speculum inserted. The vault of the vagina was inspected, and a loop of small intestine was seen to be prolapsed through the tear.

During the examination the patient suddenly collapsed. She became grey, the pulse was almost imperceptible, and the blood pressure fell to 50/0. The examination was discontinued, and within a few minutes she recovered and the blood pressure rose to its former level.

In view of the unusual type of injury and the possibility of its having been caused by an instrument of some sort, exploratory laparotomy was performed, the abdomen being opened by a midline incision. About 3 to 4 oz. (85 to 114 ml.) of blood was found in the pouch of Douglas, but there was no bleeding-point. The intestines were undamaged. The tear in the pouch of Douglas was not visible but was easily found with the finger. The uterus was small and anteverted, and both ovaries were healthy. They were not unduly atrophic.

The blood was mopped up and a drainage-tube inserted through the rent in the pouch of Douglas into the vagina. It was secured to the posterior wall of the uterus by one stitch of No. 0 catgut. The abdomen was then closed in the usual manner. A prophylactic course of penicillin and sulphonamide therapy was started after operation, and apart from a slight "spike" on the second night the patient remained apyrexial. Nothing drained from the drainage-tube, which was removed on the third day. Vaginal examination on the 18th day revealed a transverse scar in the posterior fornix. Convalescence was complicated by a stitch abscess, and the patient was discharged from hospital on the 23rd day.

A few days after operation she gave further details of the mishap. Her partner was not her husband but a man aged 30. She insisted that normal coitus had taken place in the dorsal decubitus position, and that no bizarre or unusual practices had been indulged in. She stated that her partner had been very excited, and she thought he had used too much force.

DISCUSSION

Minor injuries of the vaginal introitus due to defloration are not uncommon, and these occasionally require medical attention. More serious injuries of the vagina are rare, and Neugebauer in 1899 collected from the world literature 159 cases of injuries to the vagina sustained during coitus. Thirty-eight of these showed a posterior fornix injury. Since then four more cases of injury to the posterior fornix have been reported.

Of these 42 cases only four had the pouch of Douglas opened, and only one of these four had a prolapsed loop of intestine. Three of the four cases occurred in raped children, two being 8 years old and one 15 years old. All three patients died—two being murdered, and one dying of generalized peritonitis. The fourth case, reported by Fischer (1928), occurred in a woman of 26 who had had both ovaries removed for inflammatory disease some years previously. This patient recovered after laparotomy. The common factor in all the cases was a thin vaginal wall, due either to post-menopausal atrophy or to pre-pubertal immaturity.

The condition probably never occurs in a normal woman of child-bearing years, and should such a patient show a rupture of the pouch of Douglas one should bear in mind the probability of an instrumental injury due either to an attempt to procure abortion or to unusual sexual practices.

My thanks are due to Mr. Lewis Graham for his helpful advice in the management of this case, and to Dr. H. Nocholds and Mr. Alistair Gunn for permission to publish the case history.

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A Century of Public Health is the title of a small brochure which is being circulated abroad by the organizers of the Public Health and Municipal Engineering Congress and Exhibition which will be held at Olympia, London, from Nov. 15 to 20. The brochure traces progress from Edwin Chadwick and the first Public Health Act in 1848 to the present time. It attributes the substantial progress made first to the awakening of the social conscience and political instincts of the nation, and then to the advancement of science and the native skill and ingenuity in engineering. "For many years now," the writer states, "behind the public conscience there has been the forceful backing of engineers and industrialists eager to direct their knowledge, skill, and resources to the improvement of the public health and municipal engineering services. Nowhere else in the world was the ground more favourable for development; here was a highly industrialized country well in the van of progress in civil, mechanical, and electrical engineering and well equipped to adapt itself to the needs of the crowded communities which industry itself was creating." It is ten years since the last Public Health Congress and Exhibition were held in Britain, and the industries which exist largely for the public health and municipal engineering services will have many new developments to show.