HYPOPITUITARISM ASSOCIATED WITH INTRACRANIAL ANEURYSMS

BY

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Intracranial aneurysms may present as an acute emergency, with subarachnoid or intracerebral haemorrhage. Loss or disturbance of consciousness is usual, with neck rigidity and a blood-stained cerebrospinal fluid. On the other hand, the clinical presentation may be one of compression of the oculomotor nerves, optic nerve or chiasm, without blood leakage, and in these cases the gradual evolution of an ocular palsy or visual failure may cause considerable difficulty in diagnosis, in particular from basal intracranial tumours such as meningiomas. Compression of the optic nerve or chiasm is by no means an unusual event, and in this case an aneurysm may mimic the effects of a pituitary tumour or a meningioma. The absence of signs of endocrine dysfunction is usually regarded as an important feature in distinguishing aneurysms and meningiomas from pituitary tumours, and there is no doubt that in general this holds good.

The rarity of endocrine features in patients with basal intracranial aneurysms has encouraged us to present these three cases of intracranial aneurysm, all of which had evidence of hypopituitarism.

Methods

Serum electrolyte, urea, and cholesterol concentrations were estimated by the usual routine methods. Blood sugar was measured in capillary blood by the method of Hagedorn and Jensen (1923) and blood glucose by glucose oxidase (Marks, 1959). The glucose-tolerance test was performed after the ingestion of 50 g. of glucose. Urinary 17-ketosteroids were estimated by the method of Norymberski *et al.* (1953), and 17-hydroxycorticosteroids by the method of Appleby *et al.* (1955) with minor modifications in the dilutions of some of the solutions used. Urinary steroids were measured before and after an infusion of 25 units of adrenocorticotrophin given over eight hours on two successive days, as described by Jenkins *et al.* (1955). Urinary gonadotrophin excretion was assayed according to the method of Loraine and Brown (1959).

The basal metabolic rates were measured by the method of Du Bois and Du Bois (1916), using the normal standards of Boothby and Sandiford (1929). In Cases 1 and 3 the uptake by the thyroid gland was measured with a scintillation counter four hours after an oral dose of 30 μc of ^{131}I and expressed as a percentage of the dose given. In Case 2 the "T" test of Fraser *et al.* (1953) was employed.

The results of the laboratory investigations of the three patients are summarized in the accompanying Table.

Case 1

A spinster aged 32 was admitted to the Westminster Hospital on February 9, 1959, under the care of Dr. S. P. Meadows for assessment. She was quite normal as a child and the menarche occurred at the age of 14. Her periods were scanty but regular until they stopped suddenly at the age of 19. Three years later, in 1948, she happened to cover the right eye and discovered that she was only just able to perceive light with the left eye. She remained well otherwise until 1950, when she suddenly developed a severe occipital headache associated with vomiting. Vision in the right eye deteriorated rapidly, and when she was admitted to the Queen Elizabeth Hospital, Birmingham, under the care of Mr. J. M. Small, a week later, she was blind in both eyes. She had optic atrophy on the left and right-sided papilloedema. There was weakness of the left fourth and sixth cranial nerves, and she had complete third and fourth cranial nerve palsies on the right side. She was extremely pale, but there were no other general signs. Radiographs of the skull at that time showed a considerably expanded sella turcica, with backward angulation and erosion of the dorsum sellae. Carotid angiography showed a very large left-sided carotid aneurysm with a concave lower margin, situated above the sella. The left common carotid artery was ligated on February 7, 1950, and the left internal carotid ten days later. After this she developed temporary hyperpyrexia and vomiting, which persisted intermittently for about two years. Headaches lasted about one year. She spent four months in hospital and a further two years in bed at home before her strength slowly improved.

Results of Investigations in Three Patients with Intracranial Aneurysms and Clinical Hypopituitarism

	Case 1	Case 2	Case 3
Haemoglobin (100%=14·8 g./100 ml.)	89%	90%	75%
Serum sodium (mEq/l.)	142	130	140
,, chloride ,,	103	105	94
,, potassium ,,	3·6	4·6	4·6
,, urea (mg./100 ml.)	23	28	42
,, cholesterol (mg./100 ml.)	364	230	212
Glucose tolerance test (blood sugar in mg./100 ml.):			
Fasting	82	112	—
30 min. after glucose	126	187	—
60 ,, ,, ,,	68	—	—
90 ,, ,, ,,	84	187	—
120 ,, ,, ,,	90	175	—
180 ,, ,, ,,	—	162	—
Urinary 17-hydroxycorticosteroids (mg./24 hours):			
Day 1	1·5	6·5	2·6
,, 2	2·6	5·5	3·6
,, 3 A.C.T.H., 25 units i.v.	5·8	19·0	17·0
,, 4 ,, ,, ,, ,,	12·0	35·0	28·0
Urinary 17-ketosteroids (mg./24 hours):			
Day 1	1·0	20·0	5·0
,, 2	1·0	17·0	3·8
,, 3 A.C.T.H., 25 units i.v.	1·7	22·0	5·8
,, 4 ,, ,, ,, ,,	2·3	28·0	9·6
Water load in ml.	1,000	1,500	—
% of water load excreted in 4 hours:			
Without cortisone	25%	15%	
After ,,	161%	65%	
Urinary gonadotrophin excretion in 24 hours	<6 mg. (H.M.G.)	—	—
Basal metabolic rate	−20%	−6%	—
^{131}I uptake of thyroid as % of administered dose (normal, 15–35%)	22%	—	4%
^{131}I urine excretion as % of administered dose:			
0–8 hours	—	33·0	—
8–24 ,,	—	16·4	—
24–48 ,,	—	2·5	—
	Total "T" value	51·9 3·9	

At the time of her admission to Westminster Hospital she looked younger than her age, and was a striking picture of hypopituitarism (Fig. 1). She was very pale, with smooth skin and fine scalp hair. Her breasts were underdeveloped, and pubic and axillary hair was absent.

She was quite blind in both eyes and there was bilateral optic atrophy. There was slight impairment of elevation of both eyes, and nystagmoid jerks occurred on lateral deviation to both sides. No other abnormal signs were observed, and her blood pressure was 120/80 mm. Hg.

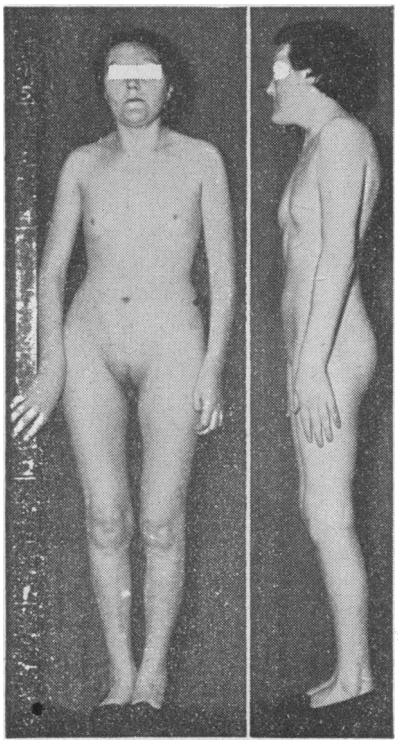

FIG. 1.—Case 1.

Radiographs of the skull showed that the sella turcica had increased in size since 1950; the anterior clinoid processes were blunted, and the dorsum sellae had now disappeared.

Urinary gonadotrophin excretion was reduced, and there was evidence of adrenal and thyroid hypofunction (see Table). Treatment was started with cortisone 25 mg. and thyroid 1 gr. (65 mg.) daily, and testosterone isobutyrate by intramuscular injection 100 mg. monthly; there was a dramatic improvement in her general condition. When last seen, on December 7, 1960, she continued to feel very well, and had started training for a job, which she had not felt well enough to do previously.

Case Report Summary.—A 32-year-old woman first noticed impairment of vision in one eye nine years previously. Two years after this she suddenly lost the sight in both eyes, at which time radiographs of her skull showed a considerably expanded sella turcica. Carotid arteriography revealed a very large left carotid aneurysm above the sella turcica, and the left common and, a few days later, the left internal carotid artery were ligated. She was severely ill, and spent two years in bed. At the time of her present admission she was quite blind and was found to have severe hypopituitarism. There was a marked improvement in her general condition after endocrine therapy.

Case 2

A single man aged 54 was referred to the out-patient department of the National Hospital on August 6, 1958, because of an attack of vertigo and vomiting. He was found to have nystagmus, and his urine contained a large amount of glucose. While awaiting admission for investigation he was referred to the West Middlesex Hospital under the care of Dr. Q. J. C. Hobson for control of his glycosuria. It was then noted that his appearance was suggestive of hypopituitarism, and a radiograph of his skull showed gross destruction of the pituitary fossa.

His haemoglobin was 101%, and two random blood-sugar concentrations were 298 and 296 mg. per 100 ml. Diabetes mellitus was diagnosed, and controlled on a 2,500-calorie diet and tolbutamide 1 g. three times a day. During the next few months he gradually reduced the dose of tolbutamide on his own accord without ill effects, and when readmitted to the West Middlesex Hospital in January, 1959, he had stopped taking it altogether. His appearance and general condition were unchanged. Fasting blood-sugar was normal, but he had a diabetic glucose-tolerance curve. A 48-hour radioiodine excretion test was within normal limits (see Table).

On January 17, 1959, he was transferred to the National Hospital under the care of Dr. John Marshall for further investigation. He had no headaches or visual disturbances, and he denied any change in his appearance, which on admission was typical of hypopituitarism. Libido had always been absent. Body hair was scanty and the pubic hair was feminine in distribution. The testicles were small and soft, and the blood-pressure was 135/80 mm. Hg. There were no other abnormal signs in the nervous or other systems. In particular, the visual fields were full.

Radiographs of the skull showed marked decalcification and erosion of the dorsum sellae, the floor of the pituitary fossa, and the walls of the sphenoidal air sinus. There was also erosion of the right anterior clinoid process and enlargement of the superior orbital fissure on that side. On lateral view a few flecks of calcification were seen overlying the fossa. A right carotid arteriogram demonstrated an aneurysm of the right carotid artery, roughly spherical and about 2 cm. in diameter, the origin of which was 2 or 3 cm. behind the cavernous sinus. A lumbar air encephalogram demonstrated a suprasellar mass. Headache, nausea, and vomiting were more severe than usual after this procedure, but were rapidly relieved on infusion of adrenocorticotrophin.

The haemoglobin was 90% and the white blood count was normal. Cerebrospinal fluid was clear and colourless, and contained one white cell per c.mm., 120 mg. protein per 100 ml., and the Lange curve was 0002221000. The W.R. was negative.

His urine was normal and sugar-free on admission, but he developed marked glycosuria following the infusion of adrenocorticotrophin, which diminished only gradually over the next few days. Urinary 17-ketosteroid excretion was within normal limits, but 17-hydroxycorticosteroid excretion was at the lower limits of normal. Both rose after the administration of adrenocorticotrophin. Diuresis of a water load, however, was greatly diminished, and was only partially improved by cortisone (see Table).

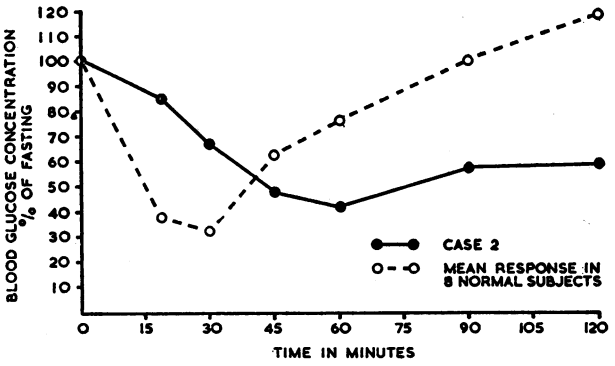

FIG. 2.—Case 2. Insulin-tolerance test. Insulin 0.1 unit per kg. body weight injected intravenously at 0 min.

An intravenous glucose-tolerance test showed an elevated fasting blood glucose and a delayed disappearance. An insulin-tolerance test showed a delayed response to insulin, with hypoglycaemic unresponsiveness (Fig. 2).

In view of the absence of neurological involvement it was thought that surgical interference was not justified, but that he should be kept under close observation. He remained

well when last heard of in December, 1960, and required no substitution therapy for his hypopituitarism, nor any hypoglycaemic agents.

Case Report Summary.—A 54-year-old man was found to have mild diabetes mellitus, which responded to oral hypoglycaemic agents. In the ensuing months his diabetes improved spontaneously, and he was found to have mild hypopituitarism. After the administration of adrenocorticotrophin glycosuria recurred. Radiographs of his skull showed enlargement of the sella turcica, and an arteriogram revealed an aneurysm of the right internal carotid artery in the region of the sella.

Case 3

A married woman aged 63 was admitted to the Westminster Hospital on July 29, 1958, under the care of Dr. S. P. Meadows for investigation of visual failure and a persistent pyrexia. As a girl she had bitemporal migrainous headaches with nausea but no visual disturbances. In September, 1956, she suddenly noticed a noise like a waterfall in the left side of her head, after which she was unconscious for four days. There was proof of a subarachnoid haemorrhage, and subsequently carotid arteriography at another hospital was said to have shown an aneurysm of the anterior communicating artery. She recovered from the subarachnoid haemorrhage but did not feel quite as fit as previously. In September, 1957, she began to complain of nausea and frequent vomiting after food. This was associated with general malaise, lethargy, and anorexia, and she lost about three stone (19 kg.) in weight. After a tentative diagnosis of myelomatosis, later not confirmed, she received a short course of prednisone, during which time she felt better.

In December, 1957, she noticed the gradual onset of visual failure, first in the right and then in the left eye. This progressed until at the time of admission she was only able to see objects a few feet in front of her. She also developed frequent severe bilateral headaches, severe anorexia, and intolerance to cold. Shortly before her admission to the Westminster Hospital she developed an intermittent pyrexia, with increasing malaise, but no localizing features apart from headaches and failing vision.

On admission she was an ill-looking white-haired woman who preferred to lie curled up in bed under numerous blankets. She was pale, with a smooth skin, and axillary and pubic hair was moderately sparse. She was slow to respond and co-operated with difficulty, but she was not confused. She had a bitemporal visual-field defect on confrontation; she could just count fingers in both nasal fields, but could see hand movements only in the temporal fields. She was unable to see Jaeger test type 20. There was slight pallor of both optic disks. There were no other abnormal signs, and her blood-pressure was 150/90 mm. Hg.

Radiographs of the skull showed slight loss of definition of the dorsum sellae and the posterior clinoid processes. Carotid arteriography showed a large lobulated aneurysm in the region of the anterior communicating artery, which filled from the left side.

The four-hour radioiodine uptake of the thyroid gland and urinary steroid excretion were both reduced (see Table). Urinary gonadotrophin excretion was not measured, and she was unable to co-operate sufficiently for her basal metabolic rate to be measured. Her haemoglobin was 87%, and her urine contained a trace of protein.

Treatment was started with cortisone 25 mg. daily, and four days later thyroid was added, working up gradually to 1½ gr. (100 mg.) daily. There was a dramatic improvement in her general condition, and when she left hospital four weeks after starting treatment she was up all day, cheerful and taking an interest in her surroundings. Her visual acuity improved, and on September 15, 1958, it was 1/60 on the left and 6/60 on the right, but her bitemporal hemianopia was still present. She has not been seen again, as she lives in Jersey, but her doctor wrote on December 9, 1960, saying that she had kept well until August, 1960, when she developed a left hemiparesis, since when she has been more or less confined to bed.

Case Report Summary.—A 63-year-old woman had had a subarachnoid haemorrhage two years before we saw her and was found to have an anterior communicating aneurysm. At the time of her present admission she had visual failure and hypopituitarism. Radiographs of her skull showed loss of definition of the posterior clinoid processes, and carotid arteriography revealed an aneurysm in the region of the dorsum sellae. After endocrine therapy there was a marked improvement in her general condition and some increase in her visual acuity.

Discussion

Clinical evidence of pituitary dysfunction is generally thought to be rare in patients with basal intracranial aneurysms (Meadows, 1951). McDonald and Korb (1939), in reviewing the symptomatology of over 1,000 cases, do not mention the occurrence of endocrine abnormalities; and aneurysms were not described as a cause of hypopituitarism in the review by Sheehan and Summers (1949). Hamby (1952) in his treatise on intracranial aneurysms mentions only briefly the possibility of hypothalamic damage by an aneurysm.

On the other hand, in patients with pituitary tumours signs of abnormal pituitary function are common. Antony Jefferson (1957) observed features of hypopituitarism in 66% of males and 37% of females in a series of 135 patients with chromophobe adenomas or craniopharyngiomas. Weinberger *et al.* (1940) considered the absence of endocrine symptoms an important diagnostic feature in differentiating aneurysms at the base of the brain from pituitary adenomas.

Although its true nature was unrecognized at the time, pituitary dysfunction associated with an intracranial aneurysm was probably first described by Bramwell (1887). The patient was a 31-year-old man with blindness, mania, scanty pubic and facial hair, testicular atrophy and gynaecomastia, in whom a huge carotid aneurysm was an unexpected finding at necropsy. The aneurysm had eroded the sella turcica, but Bramwell does not comment on the state of the pituitary gland. There was considerable softening of the base of the brain.

Few published accounts of well-documented pituitary dysfunction with basal intracranial aneurysms have appeared in the 75 years since Bramwell's paper. Patients in whom hypopituitary features predominated have been described by Lodge *et al.* (1927), Sjöqvist (1936), Jefferson (1937), Werner *et al.* (1941), Escamilla and Lisser (1942), Mecklin (1950), Schiefer and Marguth (1956), Höök and Norlén (1958), and van Staveren and Smits (1959). In most of these cases few endocrine details are available, but Driesen (1959) has described a girl of 16 years who was small and sexually underdeveloped, with well-documented hypopituitarism, and in whom an intrasellar aneurysm was successfully clipped. White and Ballantine (1961) also confirmed the diagnosis of hypopituitarism by endocrine investigations in a woman of 61, thought at first to have a chromophobe adenoma. She was later found to have an intracranial aneurysm and subsequently died. Unfortunately the necropsy report does not mention the condition of the hypothalamus or the pituitary gland.

Another case was reported by Gallagher *et al.* (1956), who described the case of a woman of 54 who was admitted to hospital with the complaint of headache. During the previous year she had also complained of polyuria and urinary frequency. She appeared ill and looked older than her years. Following an arteriogram, which demonstrated a huge aneurysm arising from the carotid artery at its bifurcation into the middle and anterior cerebral arteries, she collapsed and the blood pressure fell to 80/60 mm. Hg. Intravenous noradrenaline was given with minimal effect, but she recovered when steroid therapy was instituted. The results of subsequent laboratory investigations confirmed the clinical impression of panhypopituitarism.

The intolerance to traumatic procedures such as air-encephalography, arteriography, or craniotomy by patients with pituitary tumours is well known (Jefferson, 1957). It is salutary to remember that a similar intolerance can occur with intracranial aneurysms as in Case 2 and in the patient described by Gallagher *et al.* Presumably in each case the cause is impaired hydrocortisone secretion.

The pathogenesis of pituitary dysfunction occurring with basal intracranial aneurysms is uncertain. In the patient described by Lodge *et al.* (1927) the anterior pituitary was congested but otherwise normal at necropsy, but there was much softening of adjacent brain tissue where the aneurysm had projected into the base of the brain. Gallagher *et al.* (1956) ascribed hypopituitarism in their patient to pituitary atrophy from compression by the aneurysm acting as a large suprasellar space-occupying lesion.

This theory is unsatisfactory for several reasons. In the first place, endocrine abnormalities are rare in patients with intracranial aneurysms, including those which can be demonstrated, either surgically or radiologically, to fill the whole of an expanded sella turcica (Zollinger and Cutler, 1933; Schiefer and Marguth, 1956; Rhonheimer, 1959). Secondly, the occurrence of hypopituitarism bears little or no relationship to the size of the aneurysmal sac. The largest carotid aneurysm seen personally (R.W.H. and V.M.) was in a young woman who had borne a child six months earlier. Finally, signs of pituitary dysfunction are occasionally those, not of hypopituitarism, but of acromegaly (Bozzoli, 1937; Girard *et al.*, 1953; Brouwer, 1949; Offret and Aron, 1959), or of Cushing's syndrome (Höök and Norlén, 1958).

It seems likely that these diverse manifestations of endocrine dysfunction may be due to interference with the blood-supply of the hypothalamic nuclei, which are now believed to regulate the secretion of the pituitary hormones, since neither acromegaly nor Cushing's syndrome is attributable to damage to the anterior pituitary gland directly. Luft (1958), in discussing Höök and Norlén's patients, mentioned that atrophy of the paraventricular nucleus had been described in Cushing's syndrome. Complex endocrine changes ranging from panhypopituitarism to precocious puberty have also been described in lesions of the hypothalamus with an anatomically intact pituitary gland (Bauer, 1954). The exact abnormality probably depends upon the particular regulatory centres affected.

The vagaries of the vascular supply to the neural structures in the hypothalamus and base of the brain have been described by Dawson (1958). He found that normally each of the hypothalamic nuclei obtained its blood-supply from more than one vessel, but that the size of the vessels varied enormously in different subjects. Presumably in most cases of aneurysm there is interference with the blood-flow through some of the small arteries arising from the affected vessel. Only in those cases where the alternative blood-supply is inadequate would atrophy in the hypothalamic nuclei be expected to occur.

The possibility of endocrine dysfunction in a patient with a basal aneurysm being due to a coexisting pituitary adenoma must always be considered, and usually cannot be excluded during life unless a craniotomy is performed. The two lesions do in fact occur together (Cushing, 1912; Dandy, 1944), and three such cases, not described in this paper, have been observed at the National Hospital, Queen Square, in the past 15 years.

Summary

Three patients have been described with hypopituitarism associated with intracranial aneurysms. The possible ways in which endocrine abnormalities may be caused by an aneurysm are discussed, and it is suggested that there may be some interference with the vascular supply to the hypothalamus.

We should like to thank Dr. S. P. Meadows for his helpful criticism and encouragement, and for allowing us to use Cases 1 and 3, which were under his care in the Westminster Hospital. Mr. J. M. Small has very kindly given us particulars about Case 1 when she was in the Queen Elizabeth Hospital, Birmingham. We are grateful to Dr. John Marshall for permission to use Case 2, and to Dr. Q. J. G. Hobson for details of this case when under his care at the West Middlesex Hospital. We are indebted to Professor N. F. Maclagan and the Department of Chemical Pathology, Westminster Medical School, for the investigations in Cases 1 and 3. We should also like to thank Miss Jill Nuttall and the photographic department, Westminster Hospital, for the figures.

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Preliminary Communications

Production of Calciphylactic Facial, Oesophageal, and Mediastinal Lesions by Combined Treatment with Dihydrotachysterol and Thorium Dioxide

Calciphylaxis is a condition of hypersensitivity in which, during a "critical period" after sensitization by a systemic calcifying factor (for example, vitamin-D compounds, parathyroid hormone), treatment with certain challengers (for example, metallic salts) causes an acute local tissue-calcification followed by inflammation and sclerosis. The topical calciphylaxis thus induced by subcutaneous injection of challengers results in a cutaneous calcinosis reminiscent of calcareous scleroderma. However, in suitably sensitized (for example, dihydrotachysterol-treated) rats, calciphylactic reactions can also be elicited rather selectively at predetermined sites (for example, in the pancreas, thyroids, parathyroids, bile ducts, uterus, spleen, Kupffer cells, lungs, salivary glands, lacrimal glands) by the intravenous administration of challengers that have a particular affinity for any one organ (Selye, Cantin, and Jean, 1960; Selye, Jean, and Veilleux, 1960; Selye, Grasso, and Dieudonné, 1961).

Here we should like to report on a curious calciphylactic syndrome that can be elicited by a single intravenous injection of thorium dioxide in suitably sensitized rats.

Materials and Techniques

Forty female Holtzman rats, with a mean initial body weight of 97 g. (range, 95–102 g.), were subdivided into four equal groups and treated as follows:

Group 1, dihydrotachysterol (D.H.T., or "calcamin" ®, Wander Co.), 1 mg. in 0.5 ml. corn oil, by stomach-tube on first day. *Group 2*, "thorotrast"® (Testagar Co., a suspension containing 25 mg. of ThO_2/ml.), 1 ml., intravenously on second day. *Group 3*, D.H.T. (as Group 1) + thorotrast® (as Group 2). *Group 4*, D.H.T. (as Group 1) + thorotrast®, 0.6 ml., intravenously on second day.

The experiment was terminated on the sixth day by killing all survivors with chloroform. Specimens of various tissues were fixed in alcohol-formol (8 parts absolute alcohol, 2 parts 10% formaldehyde) for the subsequent histochemical demonstration of calcium phosphate by von Kóssa's silver-nitrate technique.

Results

The rats treated with D.H.T. alone or thorotrast® alone showed no noteworthy changes and therefore need not be discussed in detail here. Suffice it to point out that the single dose of 1 mg. of D.H.T. produced little or no metastatic calcification even in the organs (cardiovascular system, gastric mucosa, kidney) that are normally predisposed to the development of calcific

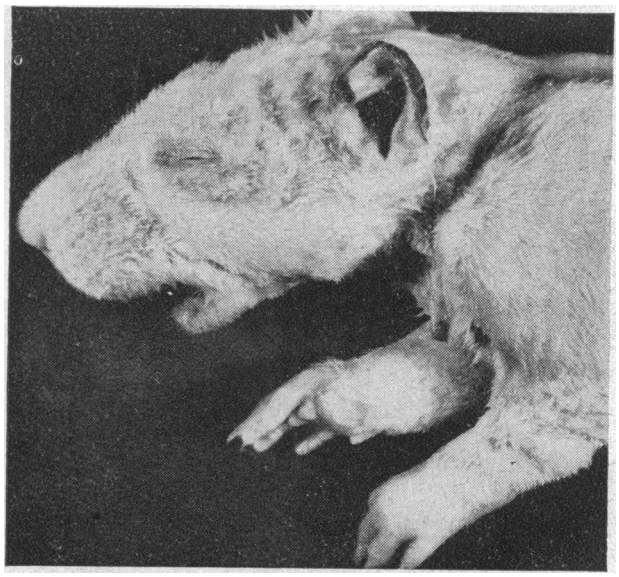

FIG. 1.—Typical aspect of the facial lesions induced by D.H.T.+thorotrast®. The fur was clipped and the left external ear removed in order to expose the swollen and calcified areas round the snout (which made it impossible for the animal to close its mouth) the eyelid, and the base of the external ear. In this instance the skin of the forepaws is also calcified, but this was rather unusual.

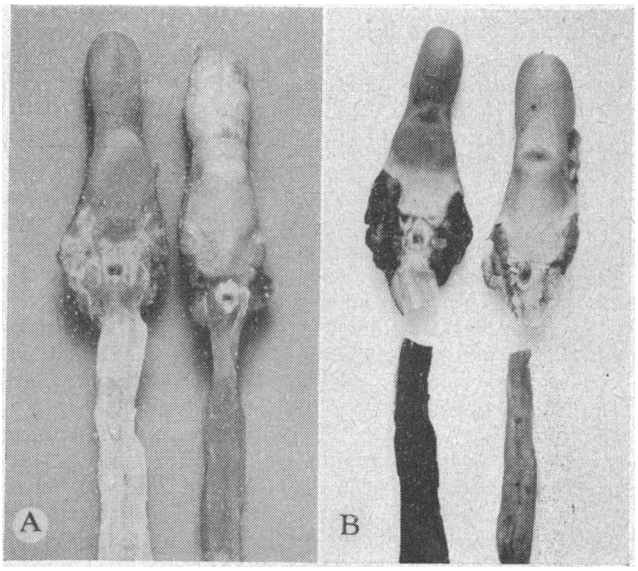

FIG. 2.—Macroscopic appearance of the pharyngeal and oesophageal lesions induced by D.H.T.+thorotrast®. A: Fresh specimens. B: After defatting and staining with $AgNO_3$. The organs on the left of each picture are those of the rat treated with D.H.T.+thorotrast®; the other specimens come from a control rat given D.H.T. alone.