generations. Cohn (1939), by assessing the weight of the exsanguinated lobes of rats, followed the effect on growth of various procedures which altered volume; he found that the weight of residual lung increased rapidly after resection and, conversely, that the normal age increase in weight did not occur if the volume of the thoracic cage was reduced by a pneumoperitoneum. It would seem that in human lungs also little if any increase in bronchiolar generations normally occurs after birth (Boyden, 1961, 1962; Reid, 1961)—that growth is distal to the terminal bronchiolus within the acinus. In hypoplastic lungs the number of terminal bronchioli and the volume of alveolar tissue are reduced. It would be expected that no correction of the bronchial and bronchiolar deficiency will occur, but that growth within the acini will be great enough to provide the lung with its normal complement of alveoli.

Summary

The features of the hypoplasia associated with congenital diaphragmatic hernia have been studied by serial section of the lungs from two newborn infants with congenital diaphragmatic hernia. The number of bronchial branchings was greatly reduced in all four lungs, the effect being greater in the ipsilateral lungs, with axial pathways giving counts of half the normal values or less, while in the contralateral lungs the count was rather more than half of the normal. Bronchial and bronchiolar regions were both affected: on occasion the bronchiolar region was completely lacking. Thus the brunt of the change falls on the bronchial tree, as the alveoli are relatively less affected, in three of the four lungs the counts being within the normal range.

The bronchial arrest is at a stage normally achieved at 10 to 12½ weeks, suggesting that at this time abdominal contents had already invaded the thorax. The arrest of bronchial branching which occurs during the "glandular" phase may be responsible for premature differentiation to the "alveolar" stage.

The nature of growth following surgical correction of the hernia is discussed in the light of experimental and anatomical studies.

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"A painting portraying an action during the Basuto rebellion of 1880-1 was presented to the Royal Army Medical College in Millbank, S.W. [on December 14], by the South African Ambassador in London, Dr. H. Muller. The action portrayed in the painting was one in which Surgeon Major John Frederick McCrea won the Victoria Cross at Tweefontein in 1881. The painting will hang in the V.C. room at Millbank, along with other Victoria Cross paintings." (*The Times*, December 15.)

CARCINOMA OF BRONCHUS WITH HYPONATRAEMIA AND DERMATOMYOSITIS

BY

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Schwartz *et al.* (1957) described the cases of two patients with carcinoma of the bronchus who developed hyponatraemia which was unlike the hyponatraemia associated with states of sodium depletion. There was no evidence of renal or adrenal disease, and yet, in spite of extreme hypotonicity of the serum, the urine remained hypertonic to serum. From the resemblance of this picture to that seen in normal subjects under the continuous influence of posterior pituitary extract it was postulated that these patients were secreting antidiuretic hormone (A.D.H.) continuously; the low serum sodium is not due to excessive loss of sodium but to abnormal retention of water. Since 1957 further reports of the syndrome in association with carcinoma of the bronchus have appeared (Roberts, 1959; Schwartz *et al.*, 1960; Dossetor *et al.*, 1961; Ivy, 1961; Turner and Williams, 1962), and the same mechanism has been postulated in central nervous system disease (Golberg and Handler, 1960; Carter *et al.*, 1961; Epstein *et al.*, 1961; Van 't Hoff and Zilva, 1961). The syndrome has also been reported in a patient without evidence of other disease (Grumer *et al.*, 1962).

Dermatomyositis often occurs with malignant disease, the association varying from 9.2% to 17.7% in the major series of dermatomyositis that have been reported (Schuermann, 1951; Curtis *et al.*, 1952; Walton and Adams, 1958; Pearson and Rose, 1960). The neoplasm may be of any type, but bronchial, ovarian, mammary, and gastric carcinomas figure largely.

This report concerns a man with bronchial carcinoma who developed both hyponatraemia and dermatomyositis.

Case Report

A 44-year-old man was admitted to Manchester Royal Infirmary on October 4, 1960. For three months he had noticed increasing breathlessness on exertion and a cough with purulent sputum. Chest radiographs showed a large left pleural effusion and a mass at the left hilum, and at bronchoscopy (Mr. D. T. Thompson) the left main bronchus was found to be occupied by a fleshy nodular tumour which proved to be an oat-cell carcinoma. Because the pleural effusion reaccumulated after aspiration it was decided that surgical treatment was not feasible and he was treated with mustine hydrochloride (nitrogen mustard). After three injections of trimustine hydrochloride ("trillekamin") the pleural effusion did not recur and he was discharged on November 11.

One week before his second admission, on January 24, 1961, he developed an erythematous rash over the butterfly area of his face, and this rash persisted. On February 21 he first complained of aching and tenderness in the muscles of the upper arms, particularly the deltoids, and over the next few days he developed oedema of his face and arms. The proximal muscles of his arms became increasingly weak, so that he had the greatest difficulty in lifting either hand to his mouth and found it impossible to brush his hair. He also complained of dysphagia, and this rapidly progressed to a stage where he had to subsist on semi-solid foods and liquids. His voice was hoarse, but the vocal cords were fully mobile. It was now apparent that he was suffering from acute dermatomyositis, and in addition to the above features

volume of fluid administered. The fluid given intravenously was 5% dextrose, but the amounts of sugar which appeared in the urine were never great enough to affect the osmolality appreciably. Alcohol is known to inhibit antidiuretic activity in the normal person (Kleeman *et al.*, 1955). In the present case 50 g. of ethyl alcohol diluted to 250 ml. and given orally at the same time as an intravenous infusion of 500 ml. of

FIG. 2.—Effects of oral and intravenous fluid loads and of alcohol on urine osmolality.

5% dextrose failed to produce a diuresis. The response to fluid loads was also observed on two occasions when he was receiving 60 mg. of prednisone daily for the treatment of dermatomyositis, and again there was failure to produce urine with a lower osmolality than serum.

Other Investigations.—Urinary 17-ketosteroid excretion was 2.5 mg./day and urinary 17-ketogenic steroid excretion 7.5 mg./day. After A.C.T.H. the urinary 17-ketosteroid excretion was 6.0 mg./day and urinary 17-ketogenic steroid excretion 30.5 mg./day. Creatinine clearance was 131 ml./minute (February 9), maximum urea clearance 102 ml./minute (February 9), and urinary creatinine 0.12 g./24 hours (March 8). Urine: persistent microscopic haematuria was present throughout the second period in hospital. The intravenous pyelogram was normal.

Necropsy

At necropsy (Dr. T. A. Cook) a mass of firm grey tumour, which had the histological appearances of oat-cell carcinoma, was found at the hilum of the left lung and there were enlarged mediastinal lymph nodes which were obviously infiltrated by carcinoma. The lungs were oedematous and pus could be squeezed from the lower-lobe bronchi on both sides. The left pleural cavity contained about 400 ml. of bloodstained fluid. There was foetal lobulation of the kidneys but otherwise no abnormality. Histology of the kidney was normal apart from a few haemoglobin casts in the distal tubules on the left side. The adrenal glands, liver, and spleen were macroscopically and histologically normal and there was no evidence of secondary deposits in the brain. Voluntary muscle from the deltoids showed no evidence of active or healed myositis.

Discussion

Sodium is the major osmotically active constituent of extracellular fluid, and, except where there is hyperlipaemia or hyperglycaemia, a low serum sodium is synonymous with low serum tonicity. Verney (1946, 1947) has shown that in the normal person a fall in serum tonicity suppresses A.D.H. activity, leading to excretion of dilute urine. Leaf and Mamby (1952) first postulated that a persistently concentrated urine in the presence of low serum tonicity is due to the continued

action of A.D.H., and this pattern can be produced experimentally in the dog (Levinsky *et al.*, 1959) and in man (Jaenike and Waterhouse, 1961). After an initial period of water retention a new steady state is achieved in which the subject remains in water-and-sodium balance but with an expanded total body water and hyponatraemia; this state can be maintained indefinitely.

In the case described above renal and adrenal function were normal. With the exception of three days at the end of the balance study, the urine remained hypertonic to plasma. Water loads administered orally or intravenously failed to produce a diuresis and there was no evidence of suppression of antidiuretic activity with alcohol. It therefore appears that the hyponatraemia was due to water retention as a result of inappropriate secretion of A.D.H. or to the presence of some other substance with antidiuretic activity.

During the period of low sodium intake the urine osmolality decreased progressively and for the three days immediately following sodium deprivation the urine was hypotonic to plasma. There was certainly a striking rise in aldosterone secretion at this time, compared with two normal subjects on the same diet, and it is possible that the high aldosterone levels inhibited the production of A.D.H. or antagonized its action. Later in the course of the illness, when large doses of prednisone were administered for the treatment of dermatomyositis, fluid loading failed to produce a dilute urine. It would appear that if there is an antagonism between adrenal cortical hormones and A.D.H. then this concerns aldosterone and not the glucocorticoids.

Dermatomyositis in association with malignant disease is probably a hypersensitivity reaction to the neoplasm. That it is due to a direct toxic effect of the growth is improbable, as dermatomyositis may develop long before malignancy becomes clinically apparent. The very satisfactory response to corticosteroid treatment in this and other cases is in favour of the hypersensitivity theory.

Summary

A patient with bronchial carcinoma was found to have a persistently low serum sodium. For a time he also had dermatomyositis, which cleared up on corticosteroids. The hyponatraemia was investigated by balance observations on a low sodium intake and the response to water-loading was observed. The results suggest that the hyponatraemia was due to inappropriate secretion of antidiuretic hormone. The only occasions on which urine osmolality fell below serum osmolality were immediately following the period of sodium depletion; it is possible that the greatly increased aldosterone activity at this time may have inhibited the production or action of A.D.H.

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CONTROLLED TRIAL OF A.B.O.B. IN MEASLES, CHICKEN-POX, AND MUMPS

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In November, 1960, a synthetic material—N¹,N¹-anhydrobis (β-hydroxyethyl) biguanide hydrochloride (A.B.O.B.)—became available in Great Britain, marketed as "virugon." It was introduced as an antiviral agent of low toxicity, claims being made that it was effective in the treatment of a wide variety of common infections, including influenza, measles, chicken-pox, herpes zoster, and mumps.

The published reports available at that time (Sjöberg, 1960; Farquhar, 1960) were somewhat difficult to evaluate but did provide sufficient evidence to justify further investigation. In view of the imminence of a measles epidemic, it was decided by the Association of Infectious Diseases Physicians to carry out a double-blind trial to determine the value of the drug in the treatment of measles and at the same time to assess its value in the treatment of mumps, chicken-pox, and herpes zoster. However, the number of cases of herpes zoster was insufficient for analysis, and no account has been taken of this condition.

Statistical Analysis

Twelve hospitals agreed to take part. The following patients were admitted into the trial: *measles*—all uncomplicated cases admitted within 24 hours of the onset of the rash; *mumps*—all cases with salivary-gland involvement admitted within four days of onset of illness; *chicken-pox*—all cases admitted within four days of onset of illness.

The measles trial ran from January to May, 1961, and the other trials from January to December, 1961. Identical numbered boxes of tablets were made up as follows:

A.B.O.B.—The active tablet contained 400 mg. of A.B.O.B. instead of the 100 mg. in the standard "virugon" tablet and did not contain the solanaceous alkaloids.

Placebo.—Starch lactose tablet flavoured to match A.B.O.B. tablet.

The active and dummy tablets were allocated to successive patients (regardless of which disease) by means of random lists held centrally.

A.B.O.B. dosage.—Adults, 400 mg. three times a day for seven days; children under 12 years, 200 mg. three times a day for seven days; and children under 5 years, 100 mg. three times a day for seven days.

Brief case histories were reported on special forms (a different form being used for each disease).

Results

Twenty-one patients were excluded from the trial, either for administrative reasons or because there was doubt about the diagnosis. Table I shows the number of cases included, together with the age and sex distribution.

TABLE I.—Age and Sex Distribution

	Total	M	F	Age					
				0-4	5-9	10-14	15-19	20-24	25-
Measles	392	202	190	284	80	2	6	10	10
Chicken-pox	100	42	58	12	22	4	10	27	25
Mumps	26	12	14	6	8	1	2	5	4

Measles.—It was realized that it would be difficult to assess any results of A.B.O.B. in a disease whose course is usually so mild; the most satisfactory criterion seemed to be the number of days between that on which the tablets were first given and that on which the temperature returned to normal. This was defined as the first day—midnight to midnight—on which the axillary temperature, recorded four-hourly, did not rise above 98.8° F. (37.1° C.). All but 9 of the 392 patients had raised temperatures when the trial started. Table II shows that

TABLE II.—Measles Results

	A.B.O.B.	Placebo
Total No. of patients	194	198
No. of days before temperature returned to normal*	3.3 ± 0.13	3.6 ± 0.15
No. of days before patient "felt well"	4.9 ± 0.23	5.0 ± 0.23
" " " " " was discharged*	13.7 ± 0.58	13.2 ± 0.44
No. of patients developing { Pneumonia	12	13
{ Otitis media	10	7
{ Other	27	28

* Mean ± standard error.

there was virtually no difference between the two groups of patients assessed, either on the temperature basis or taking account of the number of days before the patient "felt well" or was discharged. There were few serious complications, the numbers being remarkably similar in each group. The 25 cases of pneumonia complicating measles were all confirmed by chest x-ray examination. There were no cases of encephalitis. Complications shown in Table II under the heading "other" were a miscellaneous assortment of relatively mild conditions. Just under half the patients in each group were treated with an antibiotic and all but about 5% had an antipyretic. The age and sex distributions were similar in the two groups.

Chicken-pox.—Not all the patients with chicken-pox had a raised temperature on admission. Table III shows