of sodium and aldosterone possessed by amphenone. Thyroid function also was not affected. SU 4885 is much the less toxic of the two drugs, gastric disturbances being the only consistent symptom. The excessive drowsiness which severely limits the use of amphenone did not occur.

Although the action of SU 4885 on other adrenal steroids, notably oestrogens, has not yet been studied, the relatively large doses required to suppress hydrocortisone together with the formation of 11-deoxyhydrocortisone and probably deoxycortone do not indicate that this particular drug has immediate clinical application as an adrenal inhibitor. On the other hand, it seems likely that further compounds will be elaborated by means of which selective inhibition of adrenal enzyme systems may be satisfactorily achieved in patients.

Summary

The effect of a new adrenal inhibitory compound, SU 4885, has been studied in eight patients. Inhibition is directed particularly at adrenal steroid 11β-hydroxylation, so that 11-deoxyhydrocortisone (compound S) and its urinary metabolite tetrahydro-S were found in relatively large quantities in blood and urine. In sufficient dosage, orally or intravenously, SU 4885 appeared capable of reducing the levels of hydrocortisone and its urinary metabolites.

The toxicity of SU 4885 was significantly less than that of amphenone B.

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NORADRENALINE-SECRETING NEUROBLASTOMATA

BY

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Virchow (1864) was probably the first to describe neuroblastoma of the adrenal gland, referring to the tumour as a glioma. Subsequently many such tumours were described as sarcomata. Pepper (1901) regarded his case as one of lymphosarcoma with hepatic metastases. Hutchison (1907) described suprarenal sarcoma in children with metastases in the skull. Wright (1910) established the true nature of the tumour by comparing the rosettes and fibrils with those of embryonic sympathetic nervous tissue. In the light of more recent knowledge the well-known Hutchison and Pepper syndromes are no longer acceptable; Farber (1940) and Karsner (1942) failed to demonstrate any relationship between the site of metastases and the primary tumour, and Bergstrom (1937) failed to show any difference in histology.

The following three cases are pathologically neuroblastomata possessing the peculiar function of catecholamine secretion. On surveying the literature only two other cases are recorded, one by Mason *et al.* (1957) and another possible case referred to by Wilkins (1957).

Case 1

A male child aged 4½ years was admitted to the Isolation Hospital at Boksburg on May 6, 1955, with a history of abdominal pain, headache, and vomiting, which had been recurring at weekly intervals for the preceding three months, increasing in severity and culminating in a fit with left-sided twitching and a short period of unconsciousness.

On examination the child appeared acutely ill. The heart was not clinically enlarged, heart sounds were normal, and the lungs were clear. The liver was enlarged to three finger-breadths below the costal margin, and the tip of the spleen was palpable. The left side of the body was a little weaker than the right. The reflexes were present and equal. There was no neck rigidity. The cranial nerves were intact with the exception of the second, which showed bilateral papill-oedema with numerous exudates. The following day the child experienced a period of blindness lasting 15 minutes; this recurred later in the day and on this occasion lasted four hours. A provisional diagnosis of encephalitis now was made.

On lumbar puncture pressure was normal and the fluid showed no increase in cells or protein. The temperature fluctuated between 98 and 100° F. (36.7 and 37.8° C.). The child received courses of penicillin, streptomycin, and oxytetracycline.

On May 12 the blood pressure was 180/000 mm. Hg; the child was drowsy, and was transferred to the children's ward at Boksburg Hospital for further investigation.

Special Investigations and Progress

Haemoglobin, 15.5 g./100 ml.; erythrocytes, 5,120.000/c.mm.; leucocytes, 15,600/c.mm. (polymorphonuclears

86%); platelets normal; thymol turbidity ++; colloidal red ++; blood sugar, 95 mg./100 ml.; cholesterol, 150 mg./100 ml.; urea, 31 mg./100 ml. The electrocardiogram showed evidence of left ventricular hypertrophy $V_2R+V_2S=47$ mm. Blood adrenaline was 1.6 μg./100 ml., determined by the method described by Annersten *et al.* (1949). Urine examination showed protein (++), with occasional erythrocytes per high-power microscopical field. The urine contained 0.17 μg. of noradrenaline per ml., determined by the method of Goldenberg *et al.* (1954). The average urinary output was 1,400 ml./day.

The blood presssure showed no response to sedation, but fell on administration of phentolamine ("rogitine") 2.5 mg. intravenously (systolic by 24 mm., diastolic by 55 mm. Hg). A similar response was obtained with benzodioxane. *X*-ray examination of the chest revealed a mass the size of a hen's egg at the bifurcation of the aorta and subclavian artery. Skeletal survey was normal. An intravenous pyelogram showed a distorted right caliceal pattern with downward and outward displacement. A provisional diagnosis of phaeochromocytoma having been made, the chest was operated on, the mass removed, and a chylous effusion noted. During the operation the blood pressure was well controlled with phentolamine. Post-operatively the blood pressure fluctuated between 200/130 and 160/130 mm. Hg; the pleural effusion persisted for three weeks.

On section the tumour revealed the histological features of a neuroblastoma with no evidence of chromaffin tissue; a near-by lymph node showed evidence of metastatic neuroblastoma. On June 13, 1955, the abdomen was opened through a right upper paramedian incision. Marked glandular enlargement involved the right para-aortic glands and one or two on the left side, and a hard mass was palpated at the upper pole of the right kidney. The kidney was approached via a separate incision, and a large indurated right adrenal gland was removed. Post-operatively the blood pressure fell to 125/100 mm. Hg. Histological section of the adrenal showed the presence of neuroblastoma.

On June 27 the child was transferred to the Johannesburg Children's Hospital for deep *x*-ray therapy, the blood pressure having returned to 185/140 mm. Hg. He was started on vitamin B_{12} 1,000 μg. intramuscularly daily. By June 25 the blood pressure had fallen to 140/110 mm. Hg. The haemoglobin was 12.3 g./100 ml.; erythrocytes, 4,480,000/c.mm.; leucocytes, 5,000/c.mm. (polymorphonuclears 85%, monocytes 3.5%, lymphocytes 4.5%, eosinophils 7%).

The child was discharged and readmitted for deep *x*-ray therapy several times. The hypertension was persistent, and on two subsequent occasions the urine showed increased catecholamines. On March 5, 1956, a large mass was noted in the right supraclavicular fossa together with enlarged glands in the left axilla and inguinal region; the liver was enlarged to four fingerbreadths below the costal margin. At this time the blood pressure was 160/130 mm. Hg. On April 30 a 24-hour specimen of urine contained 0.9 mg. of 17-ketosteroid (measured as dehydroisoandrosterone). The blood pressure was 190/140 mm. Hg; the haemoglobin was 8.2 g./100 ml.; erythrocytes numbered 3,100,000/c.mm. and leucocytes 8,200/c.mm. (polymorphonuclears 73%, lymphocytes 16.5%, eosinophils 7%). Further deep x-ray therapy was given without response, and the patient died one week later.

Case 2

A boy aged 12 complained of pain and swelling over the middle part of his back on the right side. The pain had been present for the past few months and was increasing in severity; it was aching in character and continuous, with no definite radiation. The patient was seen by his private doctor, who later explored the region operatively, only to find erosion of the twelfth rib on the right and a mass of mushy sterile tissue above the diaphragm on that side. At operation it was noted that the right kidney felt normal. A specimen of the tissue was sent to the Institute for Medical Research for histological study, and a diagnosis of neuroblastoma was made. In October, 1957, he was referred to the Johannesburg General Hospital for further investigation and treatment.

Examination revealed a normally built intelligent boy of 12. There was no evidence of anaemia, dyspnoea, or cyanosis. His blood pressure was 110/70 mm. Hg, pulse 72, and temperature 98.4° F. (36.9° C.). There was a soft painless cystic swelling over the right frontal bone, and on deep palpation erosion of the bone was felt. The swelling had been noticed for the past three weeks and was enlarging. A scar was visible over the right twelfth rib posteriorly; the region seemed a little prominent and was dull to percussion; air entry was diminished. No abdominal mass was palpable. The rest of the examination showed nothing abnormal.

Special Investigations.—Haemoglobin, 14.9 g./100 ml.; erythrocytes and platelets, normal; leucocytes, 7,100/c.mm., with a mild absolute eosinophilia of 8%; blood urea, 27 mg./100 ml.; Wassermann reaction negative. *X*-ray examination of the chest revealed a well-defined rounded opacity above the diaphragm situated in the right posterior costophrenic sulcus and extending inwards towards the vertebral column. The outline of the pedicle of the twelfth thoracic vertebra was hazy. *X*-ray examination of the skull revealed an osteolytic lesion in the right frontal bone, the posterior border being limited by the coronal suture. Tomographic studies of the soft tissue revealed perpendicular spicules of bone radiating outward into the soft tissue, characteristic of neuroblastoma.

Progress and Further Investigations

Over the next few days the patient required methadone hydrochloride to relieve pain in the sacrum, and pain which had developed in the right thigh. *X*-ray films of the femur and sacrum revealed no abnormality at this time. An intravenous pyelogram was done, together with retroperitoneal air studies. Tomographic studies outlined a normal left kidney and adrenal gland, but no air entered the right suprarenal region. The urogram showed both kidneys to be functioning, but the upper pole of the right kidney was displaced downwards. From these findings it was impossible to determine whether the lesion was thoracic, invading the suprarenal region, or vice versa.

On the tenth day of admission there was a marked change in personality, a quiet co-operative boy becoming an excitable, restless, apprehensive individual. Later that day he was perspiring, developed retention of urine, and had a marked sinus tachycardia of 180 a minute. His blood pressure had risen to 140/95 mm. Hg. The same evening he became confused, complained of headache, and lapsed into a semicomatose state. His blood pressure was now 180/130 mm. Hg; there was no evidence of papilloedema, his breathing became irregular and shallow, and a tinge of cyanosis was evident. At this state he was placed in a respirator, and hypotensive therapy in the form of parenteral pentolinium tartrate was started. By the next morning he was breathing well, the blood pressure and pulse had returned to normal, and his state of consciousness gradually improved. The central nervous system was normal and he was able to pass urine once more; the hypotensive therapy was discontinued.

Radiation therapy was begun on the eleventh day of admission, with dramatic relief of pain and improvement in the patient's general condition. He was once more able to walk about and the lesions "melted away." The cerebrospinal fluid at this stage showed a protein of 74 mg./100 ml.; otherwise it was normal. Urine contained 0.17 μg. of catecholamines per ml., determined by the biological method of Moulton and Willoughby (1955), confirmed by the colorimetric method of Burn and Field (1956); 100 ml. of urine gave an extinction well above 0.15. Output of urine was 1,400 ml. in 24 hours. Vitamin B_{12}, 2,000 μg. daily, was given by intramuscular injection. For the rest of his stay in hospital his blood pressure, pulse rate, and mental state remained normal. There was intermittent pyrexia, which settled once the radiation therapy was under way.

For the past six months he has remained perfectly well, and repeated biochemical tests have revealed normal amounts of catecholamines. The C.S.F. protein was 27 mg./100 ml., and the blood once more shows 7,000 leucocytes/c.mm., with a 10% eosinophilia.

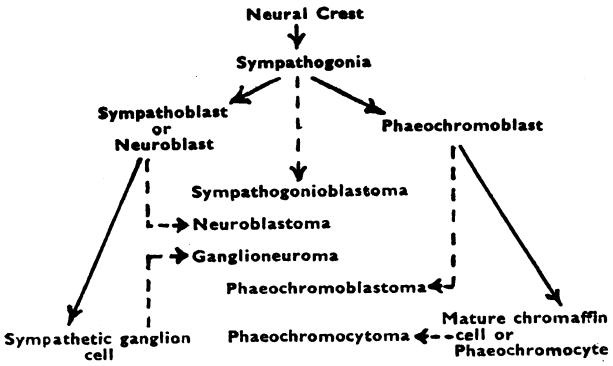
Case 3

A 4-year-old boy was admitted to the Germiston Hospital on September 26, 1957, with complaints of abdominal pain, vomiting, and swelling of the abdomen. At operation a large retroperitoneal tumour was found on the right side; a biopsy specimen was taken and the abdomen closed. When seen three days later the child was acutely ill, showing marked pallor and loss of weight. The blood pressure was 160/94 mm. Hg, pulse 100. The abdomen was very distended and tense. On palpation a large hard mass was felt in the lower right quadrant, and appeared to extend into the pelvis. The extremities were very thin. The central nervous system was normal, as were the kidneys. Histological sections of the tumour were characteristic of neuroblastoma.

The child was given deep *x*-ray therapy, but after the fourth exposure the abdominal pain became so intense that treatment had to be discontinued. The hypertension persisted throughout the illness. Biological assay of urine for catecholamines gave a value of 0.15 μg. per ml. and calorimetric extinction of over 0.15/100 ml. On October 28 the blood picture was as follows: haemoglobin, 10.5 g./100 ml.; leucocytes, 5,400/c.mm. (polymorphonuclears 73%, monocytes 5%, lymphocytes 17%, eosinophils 5%). Prednisone, 6-mercaptopurine, and vitamin B_{12} were started, but the child died one week later.

Discussion

Neuroblasts are derived from the ectoderm of the embryological neural crests, from which part of the sympathetic nervous system and adrenal medulla develop. The primitive cells of the neural crest known as sympathogonia differentiate normally into either chromaffin cells or sympathoblasts, the latter forming the sympathetic ganglion cells (see Diagram). The



tumour may arise from undifferentiated sympathoblasts wherever sympathetic nervous tissue is found, the adrenal gland being the commonest site. Occasionally the tumour is primarily thoracic (this may have been so in Case 2); Ware (1956) collected 80 such cases from the literature and noted a high incidence of neurological complications. The late presentation of some of these tumours (as in Case 2) is interesting as 80% present before the age of 5 years (as in Cases 1 and 3); exceptionally, the lesion may be present at birth. It is thought that the fully differentiated nerve cell is incapable of multiplication, and therefore in order to explain the late onset of some of these tumours one might turn to the theory of Wiesel (1902), who stated that migration and maturation of sympathogonia continue to the age of puberty. The alternative is that tumours arise from primitive cell rests.

Hypertension and tachycardia in the presence of an abdominal or thoracic mass and in the absence of renal pathology or coarctation of the aorta would suggest a diagnosis of phaeochromocytoma. The diagnosis in each case was supported by the finding of increased amounts of catecholamines. Histological section of the tumours, however, revealed no evidence of chromaffin tissue but a typical picture of neuroblastoma. From these findings one may postulate that the tumours are not in fact neuroblastomata but multipotential sympathogonioblastomata possessing a secretory ability. Primitive cells, however, possess little secretory ability, and the histological appearance is that of neuroblasts. One is then forced to accept that it is the neuroblasts themselves which are responsible for the secretion of catecholamines or for the hyperstimulation of normal chromaffin tissue; if the former is acceptable it implies that chromaffin tissue is not essential for the production of catecholamines.

The eosinophilia noted is an interesting feature and might indicate sensitivity to breakdown products of the tumour, which is prone to necrosis.

It is suggested that catecholamine-secreting neuroblastomata are not as rare as the literature indicates.

Prognosis and Treatment

In no other tumour is the prognosis so variable. Spontaneous regression has been reported by Greenstein and Berenberg (1939). Beck and Howard (1951) recorded "cure" in 47 of 475 cases—that is, 10%. Gross (1953) demonstrated an increase in the three-year survival rate since 1940, which he attributed to better operative technique and more thorough use of radiation therapy. Koop *et al.* (1955) reported a 31% 14-months survival amongst infants, which is equivalent to five-year survival in adults. Generally the younger the patient the greater the chance of survival (Koop *et al.*, 1955). The presence of secondary deposits in viscera does not alter the outlook, but bone and chest metastases indicate a poor prognosis; even in these, however, rare cases of recovery have been recorded (Andrus and Heuer, 1936). Neuroblastoma has also been known to change into the benign ganglioneuroma (Cushing and Wolbach, 1927).

Phillips (1953), reviewing 623 cases from the literature and 58 cases from the Memorial Hospital, New York, emphasized the tendency to spontaneous remission and stressed the need to do everything possible to see the patients over the malignant phase of the disease, Farber (1940) showed an increase in the survival rate following biopsy of the tumour. Wittenborg (1950) stressed the importance of irradiation, and reported that 22 out of 73 children were alive for three or more years after therapy. Radiation therapy is not contraindicated by the presence of secondary deposits. Koop *et al.* (1955) reported that the best results were obtained when as much of the primary tumour as possible was removed; he was of the opinion that irradiation was not as useful as had previously been indicated.

The fourth line of attack is the parenteral administration of large doses of Vitamin B_{12} (1,000–2,000 μg. a day). It has been shown (British Empire Cancer Campaign, 1953) that regression of neuro-

blastoma and bone metastases may occur. The exact mode of action of vitamin B_{12} in this condition is not understood.

Summary

Three cases of neuroblastoma are described in each of which the unusual power of catecholamine secretion gave rise to a clinical picture resembling phaeochromocytoma.

From the evidence presented it appears that tissues other than chromaffin are capable of catecholamine secretion.

We are of the opinion that neuroblastoma with high catecholamine secretion will prove to be not as rare as the literature suggests.

The three cases bring the total number recorded to five.

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In his report for the year 1958 Dr. Robert Aitken, Vice-chancellor and Principal of the University of Birmingham, mentions the work of the university health service. Mass radiography revealed five active cases of tuberculosis. Four of these had developed since the routine check in 1957, a fact which underlines the value of the annual chest examination for students. Dr. Aitken's report continues: "Nevertheless accidents, many on the road, rather than disease, remain the greatest single cause of lost time among students. Every year there are more student motor cars and motor cycles, and experience seems to point to the depressing conclusion that there will therefore be more accidents to students. The multiplication of vaccination campaigns of various kinds is adding yet another sizeable task to the many jobs the health service already does. Polio vaccine is now available to students, and B.C.G. vaccine against tuberculosis will probably need to be offered to larger numbers in the near future. This work is time-consuming, but its protective value is such as to make it well worth while."

RESPIRATORY DIFFICULTIES AT BIRTH*

BY

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"What have we done in resuscitation of the newborn infant in respiratory distress? We have poked, massaged, slapped, probed, struck, dilated sphincters, stimulated by physical and chemical means, jackknifed, rockered, air-locked, heated and now cooled, under- and over-oxygenated the newborn infant with an enthusiasm far beyond our knowledge of the problem." (Abrahamson, 1956.)

Prevention of respiratory distress in the newborn and resuscitation of the asphyxiated infant remain outstanding problems. The literature with its dogmatic and often contradictory opinions, and the numerous drugs, methods, and machines recommended for resuscitation, testify to our ignorance. It is proposed to review the problem of respiratory difficulty immediately after birth in the light of recent research and current opinion so that we may see what progress has been made in our efforts to gain a better understanding of the processes involved. From inability to cover every aspect, the circulatory adaptations associated with birth and the establishment of respiration have been chosen for special consideration.

Respiratory and circulatory functions cannot be separated. In the foetus the circulatory system is designed primarily to support the exchange of blood between placenta and foetus. Blood moves fastest and most abundantly to the umbilical arteries and slowly and in smaller amount to the head and lungs, but an ingenious device ensures the passage of freshly oxygenated blood to the head. The change-over at birth is dramatic, as cineradiography has shown (Barclay *et al.*, 1944; Lind and Wegelius, 1954), with a sudden increase in the speed and volume of blood flowing into the lungs. As the circulation to the lungs speeds up, so does that to the head, whereas the flow to the placenta now falls to zero. In each case it is the organ of respiration which receives the fast and abundant circulation. Clearly, anything which prevents the operation of this principle will militate against the well-being of the baby.

Function of the Ductus Arteriosus

Inspired by the pioneering work of Sir Joseph Barcroft, Dawes and his colleagues in Oxford have carried out a series of brilliantly conceived experiments to establish the course of the foetal circulation in the lamb and the changes occurring at birth. They have shown that the ductus arteriosus will contract in response to either a high arterial oxygen saturation (probably around 90%) or asphyxia, the latter operating by release of sympathetic amines. Contraction occurs within 5 to 15 minutes of birth, when asphyxia is likely to be the initial stimulus, but a satisfactory rise in arterial oxygen saturation is necessary to maintain contraction. As the ductus contracts (usually to half its original diameter), a characteristic Gibson "machinery" murmur is heard in the lamb, suggesting

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