Sera obtained from 48 R.A.F. recruits in 1960 were included in the study. These were convalescent sera from patients involved in an outbreak of respiratory infection previously described (McDonald *et al.*, 1962).

All these sera were tested for neutralizing antibodies to adenovirus type 21 in a single serum dilution (1/10) against a virus dose which caused the onset of cytopathic changes in HeLa cells in two to three days. The tests were read at four to five days.

RESULTS

A total of 27 strains received for identification were isolated between February and May, 1962—three in February, nine each in March and April, and six in May. Of these, 12 strains were received from Bristol, eight from Manchester, five from Cirencester, one each from Oxford and Wakefield.

The distribution of cases by age and clinical condition is shown in Table I. The virus was isolated from patients of all ages suffering from a wide range of respiratory diseases as well as from stools of apparently normal children. The illnesses in infants under 1 year

TABLE I.—Distribution of Adenovirus Type 21 Isolations

Age in Years	Clinical Condition		
	Upper Respiratory Infection	Lower Respiratory Infection	Normal*
<1	1	4	—
1-5	3	4	5
15+	10	—	—

* Isolated from stools.

were usually severe and were diagnosed as bronchopneumonia (2), pneumonia (1), laryngotracheobronchitis (1), and bronchiolitis (1) in an infant aged 7 months who died as the result of the infection.

Children aged 1-5 years had either a lower respiratory infection, such as bronchopneumonia, bronchitis, or bronchiolitis, or an upper respiratory infection diagnosed as a cold or pharyngitis. In this same group are included five normal children.

The clinical picture in the older patients, whose ages ranged from 15 to 65 years, was mainly mild in character and mostly diagnosed as acute pharyngitis. One patient aged 62 had a moderately severe influenza-like illness with bronchitis.

SEROLOGICAL SURVEY

The age distribution of neutralizing antibody to adenovirus type 21 is shown in Table II. It is clear

TABLE II.—Age Distribution of Antibodies to Adenovirus Type 21

Date of Collection of Sera		Age in Years			
		0-10	11-20	21-40	41+
Nov., 1961- Jan., 1962	No. of sera	94	94	140	78
	Positive (%)	2	1	18	30
April- July, 1962	No. of sera	63	45	45	43
	Positive (%)	17	15	20	28

from these findings that the incidence of antibodies to this virus is significantly greater in sera from the younger age-groups obtained after the time when this virus became prevalent. Only 2 of the 48 sera obtained from recruits in 1960 contained antibody.

DISCUSSION

It is of interest that both in Holland and in India adenovirus type 21 has been associated with outbreaks

of respiratory illness among military recruits. In this country recruits were investigated for several years up to the spring of 1960, and adenovirus 3, 4, and 7 were found to be the infecting types. Sera from these recruits examined retrospectively for antibodies to adenovirus type 21 have indicated that this virus was not in fact circulating at that time. It is probable that had there been a continuing supply of recruits outbreaks would have occurred, as has happened in other countries. As it is, the picture that emerges is of a virus causing sporadic infection in people of all ages, with the severest reactions among infants and young children.

The presence of antibodies to type 21 in the sera of adults suggests that this virus, or one antigenically similar, has been prevalent at some time in the past. The evidence available does not indicate whether it predominantly affected the younger age-groups or, following the pattern of the epidemic types of adenovirus, caused outbreaks among adult populations as has occurred recently elsewhere.

Thanks are due to Dr. Suzanne Clarke, Dr. P. G. Higgins, Dr. L. A. Little, Dr. F. O. MacCallum, and Dr. J. O'H. Tobin for sending the strains.

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Guanethidine and Phaeochromocytoma

Because guanethidine is believed to cause both release of endogenous catecholamines and augmentation of their response, it is contraindicated in patients with phaeochromocytoma (McCubbin, 1961; Page *et al.*, 1961). Genest (1960) reported on a hypertensive patient, later found to have a phaeochromocytoma, in whom intravenous injection of 0.5 mg. of guanethidine per kg. caused arterial pressure to rise to 300/190 mm. Hg and pulse rate to increase to 140/minute. Recently we had a patient with a phaeochromocytoma whose blood-pressure for over a year was well controlled with oral guanethidine. We are reporting this case to record that lowering of the arterial pressure in hypertensive patients with guanethidine need not exclude the presence of phaeochromocytoma and to obtain help in the explanation of this unusual response to guanethidine.

CASE REPORT

A 37-year-old engineer was seen by us in August, 1960, with a six-months history of throbbing headaches, especially in the morning and varying in intensity from day to day, occasional palpitation, difficulty in breathing, giddiness, nervousness, and flushing of the face. Two months prior to admission he had noticed a moderate decrease in visual acuity. He had been investigated in another hospital and given oral guanethidine 20 mg. daily with supposedly satisfactory control of the blood-pressure and symptomatic relief. Guanethidine had been stopped because of non-availability.

Examination showed an asthenic young man (weight 50 kg., height 178 cm.) in constant discomfort with frequent exacerbations of his symptoms. Blood-pressure ranged from 220/150 to 190/130 mm. Hg. There was no evidence of congestive heart failure. He had grade III hypertensive retinopathy. Electrocardiogram showed left ventricular hypertrophy, and a skiagram revealed a heart of normal size. Blood urea was 30 mg./100 ml. Routine urine examination showed no abnormality; and culture grew no pathogenic organisms. A plain x-ray film of the abdomen showed no radio-opaque calculus; the kidney was of normal size. An excretory intravenous pyelogram suggested the right upper calix to be somewhat depressed, the excretory function being normal. Phentolamine hydrochloride test (5 mg. intravenously) showed fall of blood-pressure by 30/20 mm. Hg after 90 seconds. Urinary catecholamines were reported as questionably increased.

There was a strong suspicion of phaeochromocytoma, but as there was no definite proof of its presence and as the patient was unwilling to undergo exploratory surgery it was decided to treat him with guanethidine, since he had previously responded to it. A test dose of 20 mg. (0.4 mg./kg.) intravenously caused a marked postural hypotension, the blood-pressure remaining low for the next few days. Under observation in the hospital, 20 mg. of oral guanethidine was administered daily with good response. Erect blood-pressure was maintained at 145-155 to 90-105 mm. Hg. and symptomatically the patient improved to the extent that six weeks later he resumed his full duties, continuing his treatment as an out-patient. Fundus changes regressed to grade II. Blood urea was 35 mg./100 ml.

A year later his case was reviewed, and it was decided to repeat all the previous tests for phaeochromocytoma. He was admitted to hospital and taken off guanethidine for two weeks. Phentolamine hydrochloride test (5 mg. intravenously) was very positive on two occasions (fall from 175/125 to 100/75 mm. Hg) with concurrent abnormally high urinary catecholamines—422.1 μ g. and 552.5 μ g. in 24-hour urine (normal upper limit in this laboratory is 100 μ g. in 24-hour urine). The patient now agreed to an exploratory laparotomy. He underwent operation on January 8, 1962, and a round tumour the size of a table-tennis ball, histologically a benign phaeochromocytoma, was removed from the right adrenal gland. Post-operatively his blood-pressure was stable at 120/80 to 140/85 at the time of discharge and the 24-hour urinary catecholamine excretion was 83.5 μ g. Blood urea was 32 mg./100 ml. and fundus changes of grade II hypertensive retinopathy were present. At the time of reporting the blood-pressure was normal and the patient was asymptomatic.

COMMENT

Maxwell *et al.* (1960) reported that guanethidine lowered arterial pressure of renal and neurogenic hypertensive dogs and made their arteries unresponsive to sympathetic stimulation while preserving responsiveness to noradrenaline. They suggested that hypotensive effects of guanethidine were due to failure of transmission at the neuromuscular junction of the sympathetic portion of the autonomic nervous system.

Events immediately following intravenous injection of guanethidine are, however, different from those appearing some time later and during prolonged oral administration of the drug. The immediate response to intravenous guanethidine is an abrupt rise in the arterial pressure, tachycardia, and increased cardiac output. Piloerection and contraction of the nictitating membrane accompany the pressor response in animals, and it has been suggested that these sympathomimetic effects are due to release of endogenous stores of the neurohumoral transmitter noradrenaline (Page and

Dustan, 1959), as prior depletion of endogenous noradrenaline by reserpine can abolish this pressor response. Furthermore, guanethidine causes marked depletion of noradrenaline and adrenaline from the heart and aorta of dogs (Richardson and Butterfield, 1960) and from the heart and spleen of cats and rabbits (Cass *et al.*, 1960).

Unlike the case reported by Genest (1960), the present case did not show immediate pressor response to intravenous guanethidine. Furthermore, the long-term satisfactory hypotensive effect of guanethidine in this case challenges the hypothesis of release of endogenous catecholamines by guanethidine. It is possible that the catecholamine release by guanethidine in man may be variable. Richardson and Butterfield (1960) pointed out that fluorometric analysis of plasma during the pressor response to guanethidine did not record a consistent increase in the level of circulating amines, and guanethidine introduced into the aorta just above the level of the adrenal arteries did not cause an adrenal medullary discharge. Maxwell *et al.* (1960) also showed that the chronically denervated nictitating membrane, which is supersensitive to injected noradrenaline, did not show a greater response than the normally innervated membrane during the pressor response to guanethidine. It is also not known if the endogenous store of adrenaline is the same as that employed in transmission (Page *et al.*, 1961). We have no explanation to offer, but it would appear that the hypotensive effect of guanethidine in this patient was due either to blockage of release of catecholamine or to failure of transmission at neuromuscular junction or by some other mechanism unknown to us.

We are grateful to Professor E. J. Lazaro and colleagues for successful surgery and to Professor R. B. Arora and Dr. C. N. Mathur for catecholamine estimations.

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The Executive Board of W.H.O. has adopted a resolution asking the Director-General to explore ways of making easier the exchange of information between countries on serious adverse drug reactions. The resolution also recommended that when the Sixteenth World Health Assembly meets in May it should invite countries to agree on the basic principles and minimum requirements for the toxicological, pharmacological, and clinical evaluation of drugs. It also asked that member States should report on action taken to prohibit or limit the use of a drug, and the reasons for doing so, in order that W.H.O. may immediately inform other countries. Sir George Godber was a member of the working party which drew up the resolution.