hypokalaemia with which administration of this drug may be associated (Slater and Nabarro, 1958). However, hydrochlorothiazide has little inhibitory activity on carbonic anhydrase (de Stevens *et al.*, 1958) and yet its diuretic action and the tendency to cause potassium depletion are similar (Havard and Fenton, 1959; Platts, 1959). Hydroflumethiazide also causes less bicarbonate and more chloride excretion (Edmonds and Wilson, 1959), but the tendency to produce hypokalaemia is the same (Blagg, 1959).

We have found that benzthiazide causes a loss of chloride disproportionate to that of sodium. Bicarbonate excretion was unaltered, but potassium loss in the urine occurred just as readily. In our patients with congestive cardiac failure the mean potassium excretion after benzthiazide was 54 mEq/day, compared with 59 mEq/day after chlorothiazide. Apart from this we encountered no toxic effects. The similar chemical structure of benzthiazide suggests that this drug may not be free from the occasional hazards of chlorothiazide (Nordqvist *et al.*, 1959), though the smaller dosage may be advantageous.

Summary

Benzthiazide is a new oral diuretic chemically related to chlorothiazide. The action is similar to that of chlorothiazide, and a comparison of the two drugs suggests that 100 mg. of benzthiazide is approximately equivalent to 1 g. of chlorothiazide. The action of the two drugs differed in two ways; after benzthiazide the urinary loss of chloride exceeded that of sodium, and bicarbonate excretion was not increased. In the treatment of oedema there was no less tendency to cause hypokalaemia.

We thank Dr. A. W. Spence for his constant help and encouragement; Dr. J. C. B. Fenton for much helpful advice; the consultant staff of St. Bartholomew's Hospital, who allowed us to study patients under their care; and Mrs. Eileen Akers for many of the electrolyte determinations. We also thank Miss K. Knapman and Miss M. Robinson and their nursing staff for their willing co-operation. Pfizer Ltd. suppied the benzthiazide ("fovane").

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In its *Annual Report, 1959*, the Central Council for the Care of Cripples refers to a controlled trial of the Spitz Holter valve in hydrocephalic children which it is financing—of necessity a long-term project—and to the problem of raising the standard of design and workmanship in goods made by the home-bound disabled. This is being further studied by the Council through its sponsorship of the newly formed Homecrafts Advisory Association.

INOCULATION OF HUMAN VOLUNTEERS WITH STRAINS OF COE VIRUS ISOLATED IN BRITAIN

BY

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The Coe virus was first described by Lennette, Fox, Schmidt, and Culver (1958), working in California. They inoculated into HeLa cell cultures extracts of throat swabs from military personnel suffering from mild acute respiratory illnesses. The virus was isolated from four patients, its presence being recognized by degeneration of the cultures. Antibody rises were detected in five further patients with similar symptoms. Apparently identical viruses were isolated in Britain in 1958 from the throats of four R.A.F. recruits with illnesses described as febrile cold, febrile sore throat, or influenza (Pereira and Pereira, 1959). Many more isolations were made under similar circumstances in 1959. This report describes experiments carried out with the Coe virus obtained from the throats of two patients in the 1959 outbreak.

Clinical and Laboratory Methods

In these studies 35 volunteers aged 18–45 years were used; they were housed, usually in pairs, at this unit, and were observed as described by Andrewes (1948). Specimens were collected as reported by Buckland, Bynoe, Philipson, and Tyrrell (1959).

Tissue Cultures.—Human amnion cultures were prepared as described by Zitcer, Fogh, and Dunnebacke (1955) and were maintained in medium 199. Human thyroid cultures were prepared (Pulvertaft, Davies, Weiss, and Wilkinson, 1959) in test-tubes in 20% calf serum and 0.5% lactalbumin hydrolysate in Hanks's saline, and were subsequently maintained in 2% calf serum and 0.25% lactalbumin hydrolysate in Hanks's saline. HeLa-cell cultures were prepared in test-tubes in 0.1% yeast extrast, 10% human serum, and 0.5% lactalbumin hydrolysate in Hanks's saline. The cultures were maintained in 5% rabbit serum and 0.25% lactalbumin hydrolysate in Hanks's saline. The human amnion and human thyroid cultures were maintained in a roller drum at 36° C. The HeLa-cell cultures were maintained at 36° C. in stationary racks.

The Viruses.—The prototype strain of Coe virus and hyperimmune monkey serum were provided by Dr. E. H. Lennette. These were used (*a*) for neutralization tests with volunteers' sera, and (*b*) for typing viruses isolated from the throats and faeces of volunteers. The two throat swabs to be tested were immersed in Hanks's saline which was stored at −60° C. Immediately before use the fluids were diluted in Hanks's saline, and 1 ml. of this dilution was given to each volunteer as nasal drops. Coe virus was isolated from one of the throat swabs in human amnion cultures. A further passage

TABLE I.—*Effects of Inoculating Coe Virus to Human Volunteers*

Source of Virus	Dose of Virus given (TCD_{50})	No. of Volunteers Inoculated	No. of Volunteers Yielding Virus from						No. of Volunteers in Whom there was	
			Throat on			Faeces on			Antibody Rise	Illness
			Day 2*	Day 4	Day 6	Day 2	Day 4	Day 6		
Swab 67W diluted 1/10 ..	100	4	4	3	4	0	2	1	1	4
,, 94W ,, 1/10 ..	Not titrated	3	3	3	3	0	0	1	0†	3
Second tissue-culture passage of 67W	1,000	2	2	1	1	0	1		1	2
Diluted 1/100 or 1/1,000	100	2	1	0	1	1	1		0	2
Swab 94W + antiserum ..	0	2	0	0	0	0	0	0	0	0

* Volunteers inoculated on Day 0. † Paired sera obtained from only two volunteers.

of the virus was made in similar cultures to provide a pool of second-pass Coe virus grown in non-malignant human cells. Virus from this pool diluted 1/10 was completely neutralized by Coe hyperimmune serum in a neutralization test carried out in human-embryo-kidney cultures, which were observed for 12 days.

Virus Isolation.—A total of up to 0.4 ml. of fluid from a throat swab or of 10% saline extract of faeces was inoculated into human thyroid-cell cultures. A cytopathic effect was observed within seven days or else the cultures remained healthy.

Serum neutralization tests were performed in duplicate in HeLa-cell cultures, using the strain of Coe virus designated 095 from the 1958 outbreak, and in human thyroid cultures, using 100 TCD_{50} of the prototype strain of Coe virus from Dr. E. H. Lennette. The lowest dilution of serum tested was 1/10. Virus–serum mixtures were held overnight at 4° C. and at 37° C. for four hours. 0.2-ml. volumes of the mixtures were inoculated, and the cultures were observed for two weeks.

Results

The effects of the virus on the volunteers are summarized in Table I. It can be seen that illness developed in all the seven volunteers who received virus as throat-swab material and also in the four who received the virus after two passages in cultures of human amnion cells. Virus was recovered from all volunteers who became ill, except for one receiving 100 TCD_{50} of tissue-culture-passed virus. The virus was recovered most readily from throat swabs—26 out of 33 specimens were positive; and less readily from faeces—7 of 29 specimens were positive. Seven positive throat swabs and three positive faecal suspensions were titrated in human thyroid cultures. The titres of the former ranged from $10^{1.5}$ to $10^{3.5}$ per swab (average $10^{2.4}$). The titres of the latter ranged from 10^{1} to $10^{3.5}$ per g. of faeces.

Results of serum neutralization tests were of particular interest. A rise in the content of circulating antibody was noted in only 2 of the 10 volunteers who were inoculated. Six volunteers had no detectable antibody before or after inoculation with the Coe virus. Infection occurred in spite of the presence of serum antibodies at the time of inoculation in 2 of the 11 volunteers (Table II).

The Coe virus in the fluid from swab 94W was neutralized by mixing two hours before inoculation with an equal volume of Coe antiserum at room temperature (Table I). The mixture was diluted just before inoculation to give the same final dilution of swab fluid (1/10) as in the previous experiment. The volunteers who received this inoculum were apparently not infected by the virus and did not become ill.

TABLE II.—*Variety of Antibody Responses in Volunteers From Whom Coe Virus was Recovered*

Volunteer	Antibody Titre Against Coe Virus (Strain 095)	
	Before Infection	After Infection
A*	<10	<10
B	<10	>160
C	160	640
D	320	640

* Five other volunteers shared this pattern.

The illness observed was characterized by sore throat, coryza, malaise, headache, with abdominal discomfort in some cases. In all the illnesses the clinical picture included the features of typical common colds. In four instances there was in addition an oral temperature of 99.2° F. (37.3° C.) or more—in one case reaching 100.4° F. (38° C.)—and associated general malaise and aching. The incubation period varied from two to four days (average 2.5 days). In parallel with these experiments 22 volunteers were given inocula which did not contain virus. None of them developed colds.

Discussion

Coe virus has so far been isolated from small numbers of cases of respiratory disease. As parallel control groups were not under study (Lennette *et al.*, 1958; Pereira and Pereira, 1959) the virus might have been harmless and accidentally present in the throat of persons suffering from "ordinary" colds. The present trials seem to show (*a*) that Coe virus infection and illness can be transmitted very readily to volunteers; (*b*) that the ability to produce an illness can be passed along with the virus in human amnion cell cultures; and (*c*) that neutralization of the virus by antiserum eliminates the ability to produce an illness.

We conclude that the Coe virus is pathogenic for man and causes a cold-like illness in which fever is observed more frequently than when typical colds are transmitted to volunteers. In this way it resembles the parainfluenza viruses, and, probably, the E.C.H.O. 28 (J.H. and 2060) viruses.

Summary

Seven volunteers were inoculated with Coe virus obtained direct from man, and four volunteers received virus passed twice in human amnion-cell cultures. Ten volunteers became infected as judged by recovery of virus, and 11 developed illnesses resembling the common cold. Infection occurred in spite of the presence of circulating antibody in two volunteers, and an antibody rise was detected in only two volunteers.

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DENTAL EXTRACTIONS IN PATIENTS WITH HEART DISEASE

BY

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The management of patients with heart disease requiring dental extractions is still the subject of considerable controversy. Opinions differ regarding the nature and duration of antibiotic cover, the permissible number of extractions at any one session, the choice of anaesthesia, and the need for in-patient as opposed to out-patient treatment.

Since the classical work of Okell and Elliott (1935) on the bacteriaemia induced by dental extractions, all workers are in agreement concerning the need for antibiotic cover. Penicillin still seems to be the antibiotic of choice, but opinions vary on the extent of the cover required. Thus the American Heart Association (1955) recommends the use of one injection pre-operatively on the day the teeth are removed, whereas Hobson and Juel-Jensen (1956) prefer to continue penicillin injections several days post-operatively.

Some practitioners believe that not more than one tooth should be removed at a visit, but a search of the literature has not revealed any evidence to support or disprove this contention. Hobson and Juel-Jensen (1956) and Archer (1956) recommend the admission to hospital of all patients with heart disease for dental extractions, but others do not stress the necessity for this.

As regards anaesthesia, the choice lies between general and local anaesthesia, with or without adrenaline. Mead (1951) considers that local analgesia is best and that adrenaline is not contraindicated; on the other hand, Comroe *et al.* (1954) advise local analgesia, but prefer to dispense with adrenaline. Feldman (1946) is of the opinion that no patient with heart disease need be denied the advantages of a general anaesthetic.

This paper describes the techniques in use in the dental department at the Manchester Royal Infirmary, and is based on the management of over 300 patients with heart disease. The latter were referred direct by the general practitioner or by the department of cardiology in the hospital.

Indications for Dental Treatment in Cardiac Patients

In general the indications for extraction are those used in routine dental practice. In patients with congenital lesions or rheumatic valvular disease, however, in order to lessen the risk of inducing a subacute bacterial endocarditis, extractions have often to be done where, in the normal subject, conservative therapy is the method of choice. Thus root-canal therapy is avoided in patients with apical infections; and, similarly, in patients with parodontal disease associated with mobility of the teeth, conservative parodontal therapy, necessitating frequent gum-massage, is not undertaken. A further indication for radical treatment is the presence of dental sepsis in patients suffering from subacute bacterial endocarditis. Finally, infected teeth are removed as a precautionary measure prior to cardiac surgery, preferably two to three weeks before the operation to allow adequate healing of the sockets.

Management of Patient

Preliminary Examination. — A careful dental examination is made in every case. The time so spent is used also to establish good rapport between the operator and the patient. A calm, methodical examination, conducted in a sympathetic manner, followed by a simple explanation of the procedures to be adopted, is usually sufficient to allay the fears of all but the most nervous patient. In the latter, phenobarbitone, 90–120 mg. orally four hours before extractions, or quinalbarbitone (" seconal "), 90–180 mg. orally one and a half hours before operation, is given to dispel apprehension. The newer " tranquillizers," such as meprobamate, do not appear to afford any advantage over the barbiturates. An additional advantage of the barbiturates is their ability to depress the sensitivity of the oral mucosa.

Antibiotic Therapy.—Patients with a history of rheumatic or congenital heart disease, or who gave a history of a previous attack of subacute bacterial endocarditis, were originally given 0.5 mega unit of soluble penicillin one hour pre-operatively, and the same dose was repeated two hours after extraction. Many patients failed to wait for the second injection, and so it was decided to give a single injection pre-operatively, consisting of soluble penicillin 0.5 mega unit plus procaine 0.3 mega unit. The lateral aspect of the thigh is the most convenient site for injection in dental patients. During the preliminary examination, inquiry is made regarding hypersensitivity to penicillin. Where such a history exists, the patient receives 500 mg. of tetracycline six-hourly for 12 hours before and after extraction.

Anticoagulant Therapy.—For obvious reasons this is discontinued two days prior to the extractions and is resumed the day after operation.

Anaesthesia.—Local anaesthesia is used in most patients and has been found to be very satisfactory. Its use is also convenient in a busy dental clinic. A solution of 2% lignocaine with 1/80,000 adrenaline gives adequate anaesthesia. The total amount of the solution used in any one case varied from a minimum of 1.5 ml. to a maximum of 8 ml. Routine regional anaesthetic techniques, as determined by the teeth to be extracted, are used. The more sensitive regions of the mouth, such as the upper labial sulcus and the anterior region of the palate, have a surface application of a 5% lignocaine ointment, two or three minutes before the injection of the local anaesthetic. In addition, infiltration of the buccal and lingual mucosa over the appropriate teeth is carried out. It is essential that adequate time be allowed for anaesthesia to occur, and