Absence of Anti-B from Serum.—No trace of anti-B could be found. Tests were carried out at various temperatures against cells suspended in saline solution and in albumin and with cells treated with papain. Anti-A and anti-A₁ were present and in normal amount.

Presence of B in Saliva.—The patient's saliva contains a large amount of B substance, but not quite so much as that found in the saliva of most B secretors. It also contains H substance in amount as great as that in Group-O-secretor saliva (which is greater than that found in Group-B-secretor saliva). Her saliva, as would be expected, also contains some Le^a substance.

Other Groups.—These were: MsMs, P₁, CDe/CDe, LubLub, Kk, Le(a-b+), FyaFya, and JkbJkb. The antisera used were: anti-M, -N, -S, -s, -U, -Mia, -Vw; anti-P₁, -P+P₁; anti-D, -C, -c, -C^w, -E, -e, -V; anti-Lu^a, -Lu^b; anti-K, -k; anti-Le^a, -Le^b; anti-Fya, -Fyb; anti-Jk^a, -Jk^b.

It is difficult to believe that such an extraordinary ABO group finds itself merely by chance in a body so extraordinary in other ways. It seems reasonable to expect that in time the two conditions will be seen to be connected.

Discussion

The mechanism by which the XX chromosome pair causes the female gonad to be developed in preference to the male is unknown; therefore it is not possible to do more than speculate as to the causes leading to the development of testicular and ovarian tissue in the same individual. Freemartins in cattle and swine may develop testicular and ovarian tissue in the presence of a normal set of chromosomes. Domm (1939) has reported that female chicks produce a testis if the ovary is removed soon after hatching. Evidently it is not necessary in every case to postulate a genetic cause for hermaphroditism. In the present case, however, the association between the excessively rare ABO blood group findings, which must be genetic, and the hermaphroditism leads one to search for a genetic mechanism capable of producing both findings at one stroke.

Plunkett and Barr (1956) discussed the possible causes leading to sex-chromatin findings in skin and neutrophils similar to ours in two cases of Klinefelter's syndrome. They suggested that an X chromosome may have been involved in a reciprocal interchange or translocation. The ABO blood group findings suggest that the patient may be homozygous for a gene interfering with the function of the B genes in a way analogous to the action of the genotype yy described above. Perhaps our patient is in reality heterozygous for the interfering gene, but the action of the normal dominant allele is lost because it is on the other chromosome involved with X in a reciprocal translocation.

Summary

A further report is made on a case of true hermaphroditism of which a clinical account has already been given.

The skin and oral mucosa are chromatin-positive. The internal genitalia are chromatin-positive, but the typical chromatin mass is smaller and less frequent than usual. Two to three neutrophils per 500 counted displayed the typical female "drumstick."

The blood group is O, but there is no anti-B substance in the serum. The patient is a secretor, and B substance is found in the saliva and urine.

It is suggested that reciprocal interchange between an X chromosome and an autosome carrying a gene necessary for the placement of B on the red blood corpuscles is responsible.

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FULMINATING STAPHYLOCOCCAL PNEUMONIA ASSOCIATED WITH INFLUENZA VIRUS C

REPORT OF A FATAL CASE

BY

C. S. DARKE, M.D., M.R.C.P.

Consultant Physician, City General Hospital, Sheffield

P. H. WATKINS, B.M., B.Ch.

Medical Registrar, City General Hospital, Sheffield

AND

J. E. M. WHITEHEAD, M.B., Dip.Bact.

Deputy Director, Public Health Laboratory (M.R.C.),
Sheffield

Taylor (1949) first isolated influenza virus C in 1947 from a patient suffering from a mild influenzal illness. The occurrence of this virus in human illness which has been recorded since then (Francis *et al.*, 1950; Fukumi *et al.*, 1951; Styk, 1954; Minuse *et al.*, 1954; De Meio *et al.*, 1955; Andrews and McDonald, 1955) has shown that it is usually associated with mild or trivial infections of the respiratory tract. A few authors have, however, described more severe illness. Gerber *et al.* (1952) isolated the virus from U.S. naval recruits in whom "pneumonia of unknown aetiology" was diagnosed; Grist (1955) found serological evidence of infection in four adults admitted to hospital with a diagnosis of pneumococcal pneumonia; and Librach (1956) described the cases of two patients with "severe bronchopneumonia" in whom infection by influenza virus C was diagnosed on serological grounds. None of these infections, however, proved fatal.

The occurrence of fulminating staphylococcal pneumonia complicating infections by the influenza viruses A and B is well recognized (Stuart-Harris, 1953). This paper describes a fatal case of *Staphylococcus aureus* invasion of the lungs in association with influenza virus C, which was isolated 18 hours before death.

Case Report

A housewife aged 46 was admitted to hospital at 7 a.m. on July 6, 1956, because of severe dyspnoea from an extensive pneumonia. Her previous health had been good until the preceding week, when she had developed a mild infection of the upper respiratory tract. She did not take

to her bed, but when first examined on July 5 she was found to have consolidation of the left lower lobe and the base of the right lower lobe, for which "sulphatriad," 1 g. every four hours, was prescribed. During the night she became desperately ill with increasing cyanosis and dyspnoea. On arrival in hospital she looked extremely ill. She was drowsy, pale, and moderately cyanosed. The axillary temperature was 100° F. (37.8° C.), the radial pulse was just palpable at 140 a minute, and respirations were shallow and rapid, varying between 50 and 60 a minute.

Physical examination was difficult owing to marked respiratory distress. There was diminished expansion of the left side of the chest, over which the breath sounds were weak and associated with fine rales. The percussion note appeared hyperresonant. Rales were also audible at the right base. The blood pressure was 90/60 mm. Hg. The heart sounds were normal. There was no herpes.

It was thought possible that she had developed a left pneumothorax, but a portable chest radiograph showed no evidence of this and revealed instead extensive consolidation of a patchy character throughout the left lung and similar though less marked disease in the right lower lobe.

A tentative diagnosis of fulminating staphylococcal pneumonia complicating an influenza virus infection was made and steps were immediately taken to combat the overwhelming infection. Chlortetracycline (aureomycin), 0.5 g., was given intravenously, and 2 ml. of nikethamide every hour. Her condition deteriorated rapidly, and two hours after admission the picture resembled a state of profound shock with generalized heliotrope colour and extreme tachypnoea. The systolic blood pressure had fallen to 60 mm. Hg. A nor-adrenaline intravenous drip was started and the patient was placed in an oxygen tent. Chlortetracycline was continued intravenously and crystalline penicillin, 2 million units, was given intramuscularly every six hours. She also received three injections of 20,000 units of staphylococcal antitoxin intravenously.

With these measures her colour and breathing improved and the blood pressure rose to 105/75 mm. Hg. Throughout this period there was no cough or sputum, but the breathing was "bubbly."

Unfortunately the initial response was not maintained and she died at 3.20 a.m. on July 7, 20 hours after admission.

Laboratory Investigations.—On admission the haemoglobin was 94% and the leucocyte count 5,000 per c.mm. The differential count was: segmented neutrophils 15%, band cells 12%, metamyelocytes 3%, myelocytes 2%, monocytes 15%, and lymphocytes 53%. As the patient was too ill to expectorate any sputum, a throat swab was taken. No organisms were seen on the direct films and culture was sterile. A blood culture taken on admission remained sterile after incubation for five days. Throat swabs were taken into 50% skimmed-milk-saline and into tissue-culture maintenance medium for virus isolation, and blood was collected for serological examination. From the throat swab in milk-saline influenza virus C was isolated (see below).

Post-mortem Examination

The examination was made 56 hours after death, and nothing abnormal was found externally. Apart from toxic

changes in the liver the internal examination showed that the pathological changes were confined to the respiratory system. There was no adrenal haemorrhage.

The bronchi were congested and there was ulceration of the lower part of the trachea. The right lung was deeply congested and the left lung showed almost complete consolidation. On section, firm pneumonic areas were visible, interspersed with congested spongy lung. Within the more solid areas there were small beads of yellow pus, but no actual cavitation. The whole picture was one of a diffuse staphylococcal lobar pneumonia, and this was supported by the histological findings.

Microscopical examination of various sections of the lung showed areas of pneumonic consolidation mostly in the stage of red hepatization. Elsewhere the alveoli were filled with oedematous fluid and the capillaries were extremely congested. The bronchial walls showed an acute inflammatory reaction.

Culture of material from the lungs and bronchi yielded a heavy, almost pure growth of *Staph. aureus* (coagulase positive) which was sensitive to penicillin, streptomycin, erythromycin, chlortetracycline, chloramphenicol, sulphadiazine, and sulphadimidine. The strain of *Staph. aureus* was examined for its reaction to bacteriophage, using the phages and methods of Williams and Rippon (1952), the phage filtrates being kindly supplied by Dr. R. E. O. Williams, of the Staphylococcal Reference Laboratory, Colindale. It was found to give a weak reaction only with undiluted phage 55.

Examination of Contacts

Ten days after the patient's death her personal contacts were investigated to discover whether there was any clinical or laboratory evidence of infection by respiratory viruses, and whether they harboured the same phage type of *Staph. aureus*. The persons living in the patient's household or with whom she had close contact were her husband (aged 51), her mother (aged 71), her daughter (aged 24), her son (aged 17), her grandchild (aged 11 months), and a friend (aged 64). In none, apart from the son and grandchild, was there a history of recent respiratory infection. The grandchild was found to have had a nasal discharge for the previous two or three days, but was otherwise healthy. The son had been vaguely unwell for a fortnight and had complained of sore throat and enlarged glands in the neck for the previous four days. On examination he was found to have generalized enlargement of the lymph nodes and a readily palpable spleen. A diagnosis of glandular fever was made, and was confirmed by the finding of a positive Paul-Bunnell reaction to a titre of 1/112 after absorption with guinea-pig kidney and by the finding of 25% of "glandular fever" cells in a total leucocyte count of 7,400 per c.mm.

Blood was collected for serological examination from all the contacts except the grandchild. Throat swabs for virus isolation were taken from the son and grandchild, as they showed respiratory symptoms. Broth-moistened swabs were taken from the anterior nares for isolation of *Staph. aureus*, by direct plating on blood-agar and by enrichment culture

Results of Investigations of Patient and Contacts

	C.F. Titres*								H.I. Titres*		Nasal Swabs	
	Influenza A	Influenza B	Influenza C Strain 1233	Influenza C Patient's Strain	"Influenza D"	Adeno-virus	Psittacosis	R. burneti	Influenza C Strain 1233	Influenza C Patient's Strain	<i>Staph. aureus</i> Isolated	Phage Type
Patient ..	<8	<8	<8	<8	<8	<8	<8	<8	40	40	+ from lung	55 (w)
Husband	<8	<8	<8	<8	<8	<8	20	<8	80	40	—	—
Mother ..	<8	<8	<8	<8	<8	<8	<8	<8	<10	20	—	—
Son ..	<8	16	<8	<8	<8	<8	<8	<8	80	80	—	—
Daughter	<8	<8	<8	<8	<8	<8	<8	<8	80	40	+	Untypable
Grandchild	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	+	—
Friend ..	<8	<8	<8	<8	<8	<8	<8	<8	160	120	+	6/7,47/53/54

* Titres expressed as reciprocals. NT = Not tested.

in 10% salt cooked-meat broth (Maitland and Martyn, 1948). The results of these investigations are summarized in the Table.

Virological Investigations

Virus Isolation

For isolation of virus the medium into which the swabs had been collected was inoculated in 0.1-ml. amounts into the amniotic sac of six 11-day fertile hens' eggs, and in 0.5-ml. amounts into two tubes of monolayer tissue cultures of human epidermal carcinoma cells (strain HeLa). After the eggs had been incubated for three days at 36° C. the amniotic fluids were harvested, tested for haemagglutinating activity against human and fowl red cells, and re-inoculated into a further six eggs. Three such passages in eggs were made for each specimen. No haemagglutinating activity was found, except in the second- and third-passage eggs inoculated with the patient's throat swab collected in milk-saline. None of the tissue cultures showed any cytopathic effect after incubation at 37° C. for seven days on either the first or second passage, nor was any haemagglutinin detected in the tissue-culture fluids.

Further tests on the positive amniotic fluid showed that the haemagglutination was due to a strain of influenza virus C. The characteristic property of agglutinating red cells to higher titre at 4° C. than at room temperature, and of agglutinating fowl cells to higher titre than human cells, was observed. Feeble agglutination of guinea-pig red cells was also noticed with the early passage material, as described by Taylor (1951) for the strain 1233, but this property was lost on subsequent passages. Specific complement-fixation was shown to occur between dilutions of the amniotic fluids and sera known to contain antibody against influenza virus C. No complement-fixation could be demonstrated in tests with known positive influenza A and influenza B sera, nor was any observed with a serum known to fix complement strongly with "influenza D" (Sendai) virus (Kuroya *et al.*, 1953; Jensen *et al.*, 1955).

The identification of the virus as influenza virus C was kindly confirmed by Dr. L. A. Hatch, of the Virus Reference Laboratory, Colindale, by whom its international reference designation, C/Eng/293/56, was allocated.

Serological Examinations

Two kinds of serological examinations were made, complement-fixation (C.F.) tests and haemagglutination-inhibition (H.I.) tests. The C.F. tests were performed on "perspex" sheets by a method based on the technique described by Fulton and Dumbell (1949), in which overnight fixation at 4° C. is used. A five-volume test, using 0.02 ml. as the unit volume and 2 units of complement, was employed. Sera inactivated at 56° C. for 30 minutes were tested by this means against the following antigens issued by the Standards Laboratory for Serological Reagents, Colindale: influenza A (soluble), influenza B (soluble), influenza C, adenovirus group, psittacosis—L.G.V., and *Rickettsia burneti*. The sera were also tested against the patient's strain of influenza virus C, using undiluted amniotic fluid as antigen, and against a strain of "influenza D" (Sendai virus) kindly supplied by Dr. D. A. J. Tyrrell, of the Virus Research Laboratory, Lodge Moor Hospital, Sheffield, using high-titred allantoic fluid as antigen.

H.I. tests were performed at 4° C., using plastic haemagglutination plates (W.H.O., 1953), with, as antigens, amniotic fluid from eggs inoculated with influenza virus C strain 1233, kindly supplied by Dr. B. E. Andrews, of the Virus Reference Laboratory, Colindale, and similar material from eggs inoculated with the patient's strain of virus. Four 50% agglutinating doses of virus were used and sera were inactivated for 30 minutes at 50° C. before testing. Prior treatment with *Vibrio cholerae* filtrate was not undertaken, since it has been shown by Hilleman and Werner (1953) that human sera do not possess heat-stable inhibitors against influenza virus C. The results of these tests are shown in the Table.

Discussion

From the clinical aspect, the interest of this case lies in the fact that, although it occurred out of season, the condition was recognized on admission to hospital and appropriate treatment was begun immediately to combat the extensive pneumonia and profound toxæmia. Previous experience of infections due to influenza virus A complicated by staphylococcal pneumonia had shown the urgency of parenteral antibiotic therapy and the need to alleviate as far as possible the circulatory collapse. Despite such measures the response was only temporary. Removal of the bronchial secretions by the patient's own efforts was clearly impossible owing to the stuporous state, and mechanical cleansing by aspiration could hardly have proved effective. Oxygen relieved the state of hypoxia but did nothing to relieve the intense toxæmia. Although staphylococcal antitoxin was given intravenously its apparently favourable effect proved to be transitory and it failed to prevent a fatal outcome. It would appear that a stage is quickly reached when such measures are of no avail.

Culture of the sputum or a throat swab from these cases usually yields *Staph. aureus* in abundance. The negative result in the above case may be accounted for by the marked prostration, "bubbling" respiration, and ineffective cough which were such prominent features. Nevertheless, *Staph. aureus* was isolated in heavy, almost pure culture from the lungs and bronchial secretions after death, and was shown to be fully sensitive to the antibiotics administered. The strain isolated in the present case reacted with a bacteriophage of group II. This reaction was given by only 14% of the strains of *Staph. aureus* isolated from cases of influenza pneumonia in the series reported by Williams *et al.* (1953), in which most of the strains were found to react with phages of group I.

Whether there is a particular phage group association with influenza virus C infections, as apparently occurs with influenza virus A and B, is not known. Although influenza virus C does not possess the marked ability to spread in epidemic form which is characteristic of influenza viruses A and B, the surveys of antibodies which have been made in this country (Andrews and McDonald, 1955; Grist, 1955; Balducci *et al.*, 1956) indicate that many persons have been infected in childhood or early adult life. In the contacts studied, the sera from four persons showed raised H.I. titres and none showed a raised C.F. titre. These findings indicate that these individuals had been infected by influenza virus C at some time, but, since no raised C.F. titres were found and no virus was isolated from the two contacts with respiratory symptoms, there was nothing to show that these infections had been acquired recently.

This report serves to emphasize the problem of fulminating staphylococcal pneumonia, which is a well-recognized complication of infection by influenza viruses A and B, and which may, as in the present case, complicate the usually milder infections by influenza virus C. In any case of pneumonia rapid deterioration leading to a state of shock should raise immediate suspicion that the patient belongs to this group and every available resource should be employed as a matter of urgency.

Summary

A case of fulminating pneumonia in a middle-aged woman due to a penicillin-sensitive strain of *Staph. aureus* is described in which death occurred despite intensive antibiotic and antitoxin therapy. In four of six household contacts serological evidence of past infection by influenza virus C was obtained, but no evidence was found to show that the infections had been acquired recently. None of the contacts harboured the same phage type of staphylococcus as the patient. The importance of prompt recognition of the condition and the urgency of instituting adequate therapeutic measures are stressed.

We are indebted to Dr. A. J. N. Warrack for his report on the post-mortem examination, and to Dr. E. H. Gillespie for phage-typing the staphylococci. We thank Dr. L. A. Hatch, of the Virus Reference Laboratory, Colindale, for confirming the identity of the strain of virus isolated; Dr. G. S. Wilson for his helpful criticism; and Mr. P. M. Hinchliffe, Mr. M. W. Scruton, and Mrs. B. Newton for technical assistance.

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PROTOVERATRINE A IN TREATMENT OF HYPERTENSION

BY

IAN R. GRAY, M.D., M.R.C.P.

Consultant Physician, Coventry Group Hospitals; Late Senior Registrar, National Heart Hospital, London

AND

NEIL A. J. HAMER, M.B., M.R.C.P.

Registrar, National Heart Hospital, London

Extracts of the *Veratrum* plants cause a fall in blood pressure and bradycardia through the vagal reflex described by von Bezold and Hirt (1867) and by Jarisch and Richter (1939). Their use for the treatment of hypertension has been limited by the frequent occurrence of nausea and vomiting. Trials have suggested that certain of the pure veratrum alkaloids might lower the blood pressure with less emetic effect (Hoobler *et al.*, 1952a). A study of protoveratrine, the principal alkaloid of *Veratrum album*, was therefore undertaken. This has been shown to be a mixture of two closely related ester-alkaloids, protoveratrine A and protoveratrine B (Stoll and Seebeck, 1953; Nash and Brooker, 1953).

Parenteral administration of protoveratrine to patients with hypertension causes a fall in blood pressure with bradycardia (Meilman and Krayner, 1949). This is accompanied by vasodilatation in the limbs, and the cardiac output is not consistently altered (Hoobler and Corley, 1950). Renal blood flow remains constant or is increased, but with considerable falls in blood pressure the glomerular filtration rate is diminished (Hoobler *et al.*, 1952b).

Methods

The effect of protoveratrine preparations was studied in patients with hypertension admitted to hospital for assessment. All blood pressures were taken by one or other of us and the value recorded was the lowest of three successive readings. Oral test doses were given daily after the patient

had been resting for an hour, the blood pressure being observed during that time. Pulse and blood pressure were taken every 30 minutes for the next four hours and hourly thereafter.

The initial amount given was 0.25 or 0.5 mg. of protoveratrine A, and successive doses were increased by 0.25 mg. until a satisfactory response was obtained. With intravenous administration, blood-pressure readings were taken each minute for 15 minutes and at longer intervals thereafter, or, alternatively, a continuous record was made from an indwelling arterial needle. Blood-pressure readings after resting in bed for 10 minutes were taken at 9 a.m. each day throughout the patient's stay in hospital. The average of the first three daily readings before treatment was taken as a baseline for subsequent out-patient assessment.

Out-patients on treatment with protoveratrine A were seen every two weeks at first and later every four or six weeks. The blood pressure recorded was the lowest of three measurements made after resting on a couch for 5, 10, and 15 minutes.

Activity of Protoveratrine A and B

The response to intravenous injection of protoveratrine was studied in nine patients with hypertension. In several of these patients a continuous pressure record was obtained with an indwelling arterial needle. After an injection of 0.15 to 0.21 mg. of protoveratrine the blood-pressure and pulse rate gradually fell, reaching their lowest levels in about 10 minutes. A substantial fall in blood pressure occurred in every case. Blood pressure and pulse rate returned to their original levels in two to three hours (Fig. 1).

FIG. 1.—Effect of intravenous protoveratrine A (0.18 mg.) on blood pressure and pulse rate in a man aged 55 and weighing 75 kg. (Case 1).

Patients were usually aware of a feeling of warmth in the chest and arms as the blood pressure fell, and occasionally hiccup occurred, but there was no nausea or vomiting. A further fall in blood pressure sometimes took place if the patient stood up while the hypotensive effect was at its greatest. The response of the blood pressure and pulse to Valsalva's manœuvre was, however, preserved. The response to intravenous protoveratrine was the same using protoveratrine A, protoveratrine B, or a mixture of the two alkaloids (Table I).

The amount of protoveratrine taken orally which caused a fall in blood pressure varied widely from patient to patient.

TABLE I.—Response to Intravenous Protoveratrine

Proto-veratrine	No. of Tests	Average Dose in μ g./kg. Body Weight	Average Initial B.P.	Average B.P. Fall
Mixture ..	3	3.2	193/102	81/42
A ..	5	2.3	197/126	64/44
B ..	4	2.3	231/128	65/24