Mr. M. Silverstone) for permission to publish Case 3. Professor T. N. A. Jeffcoate saw both these cases and refers briefly to Case 3 in his *Principles of Gynaecology*.

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ACUTE RESPIRATORY DISEASE IN THE R.A.F., 1955-7

BY

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In a survey of acute respiratory disease in the Royal Air Force in the winter of 1954-5 (Andrews *et al.*, 1956) about half the admissions to sick-quarters with a respiratory illness were due to influenza B, which was prevalent in the United Kingdom at that time. Identifiable virus infections caused only a small proportion of the remainder, but an outbreak due to adenovirus infection was found in one of the ten stations observed (R.A.F., Stafford) and had been responsible for a few cases in another station (R.A.F., Kirkham) just before the survey began. Three of the six strains of adenovirus isolated from these two stations were examined for type: one was type 4, one type 14, and one was untypable by any of the sera then available. Several investigations in American service units have shown that adenovirus infections are most prevalent among recruits (Hilleman *et al.*, 1955; Berge *et al.*, 1955; Rowe *et al.*, 1956; Woolridge *et al.*, 1956; Hilleman *et al.*, 1957). Further surveys were therefore made during the winters of 1955-6 and 1956-7 aimed at defining more clearly the importance of influenza virus and the adenoviruses in causing acute respiratory disease and invaliding from the Service.

Materials and Methods

1955-6.—At 25 stations in England and Wales a standard record card was completed by the unit medical officer for every patient admitted to station sick-quarters for over 48 hours between October, 1955, and April, 1956. Four of the stations were for apprentices or boy entrants aged from 15 to 18 years; the remainder were operational units. In all cases of acute respiratory disease an attempt was made to obtain 5 to 10 ml. of blood on admission, and a further specimen 14 to 21 days later. Paired sera were obtained from 1,394 patients—70% of all those admitted with an acute respiratory illness at these stations. The proportion of illnesses tested from boys' units was 58% and from operational units 79%. In addition, at four recruit stations record cards and paired blood samples were requested from up to 10 recruits admitted each week with an acute respiratory illness. A total of 281 paired sera were thus obtained, representing 8% of acute respiratory admissions at these stations. Throat swabs for virus isolation were taken from a few recruits whenever there was evidence of an outbreak. The ends of the swabs were broken off into 5-ml. bottles containing 2 ml. of virus transport medium (0.5% lactalbumin hydrolysate in Hanks's solution) and taken to the laboratory on solid carbon dioxide.

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The institution of Fire Engineers has had prepared three coloured filmstrips, with lecturer's notes, on fire precaution in hospitals. The first deals with the causes of fire, the second with fire-fighting and means of escape, and the third with the evacuation of patients. The filmstrips and notes were made by the department of medical illustration of the South Manchester Hospital Group and the Manchester Royal Infirmary in collaboration with the Manchester Fire Brigade, and are intended primarily for nursing staff. Whilst fire brigades can arrange periodic inspections of hospital premises, technical experts on fire prevention are not always free to fit in with hospital training courses. It is hoped therefore that the filmstrips and notes will provide useful material for the lay lecturer. Each filmstrip (with its notes) costs two guineas, and copies are obtainable from Chantry Publications Ltd., 63, Neal Street, London, W.C.2. In 1956, according to figures from the Joint Fire Research Organization, there were 452 fires in hospitals in England and Wales, 32 in Scottish hospitals, and 8 in hospitals in Northern Ireland. The commoner causes, from a 5-year analysis of fires in hospitals and homes and institutions for the care of the sick and infirm, were smoking (18.3%), electric apparatus, heaters, and fires (14.3%), fires in grates (11.5%), gas apparatus (9.3%), electric wiring (6.3%), and slow combustion stoves (5.9%).

1956-7.—The scope of the investigation was changed during this period. At two recruit stations, between November, 1956, and April, 1957, throat swabs were taken from all patients admitted to sick-quarters with respiratory illness for more than 48 hours; standard record cards were again completed by the unit medical officer. At one of these stations all patients had their chests radiographed within seven days of admission, and paired samples of blood were taken from all patients with evidence of pneumonia. Detailed results of this study are to be reported elsewhere (J. N. C. Cooke and J. Gilroy, 1958, personal communication). At two other recruit stations visits were made by one of us at two-weekly intervals. Throat swabs and records were obtained at this time from all patients admitted with acute respiratory illness within the previous 48 hours. Twenty-seven other stations of various types—boys' units, technical training schools, and operational units—notified their weekly incidence of respiratory disease. Whenever there appeared to be an outbreak the station was visited and a number of patients were examined and records and specimens obtained.

Records of Invaliding.—The records were examined of all Service men with more than two weeks' service invalided in 1953 and 1954 for any respiratory illness except tuberculosis and cancer.

Laboratory Methods.—Throat swabs and sera were stored at -30°C . until tested; details of the tests used have been described previously (Kendall *et al.*, 1957) and are therefore only outlined here. Serological diagnosis was made by means of the complement-fixation test. Partially purified soluble antigens prepared in fertile hens' eggs were used for influenza viruses A and B, and heated but otherwise untreated fluids from HeLa cell cultures infected with RI-67 (adenovirus type 4) were used as the adenovirus group antigen. Adenovirus isolation tests were done in HeLa cell tube cultures which were kept a minimum of 10 days before being reported negative. Adenovirus strains were identified by the complement-fixation test and were typed in HeLa

cell cultures by neutralization tests using specific rabbit sera. Two hundred and fifty-seven serum pairs, comprising almost all those collected between February 10 and March 19, 1958, were also tested by Dr. P. S. Gardner for evidence of Sendai virus infection (Gardner, 1957).

Results

1. Prevalence of Respiratory Illness

Fig. 1 shows respiratory disease admission rates for periods of four weeks in various types of unit in the two winters studied. Incidence was highest in recruit stations in both winters, reaching 9% to 10% of the population at risk, but persisting longer in 1955-6 than in 1956-7. Non-recruit units had a much lower incidence, rising to just over 1% in February, 1956, and in March, 1957. Admission rates in boys' units lay between these two, and ranged from 2% to 6%; rates were high in the autumn of 1955, in March, 1956, and in February, 1957.

2. Laboratory Results

1955-6.—In recruit units, of 281 pairs of serum tested, 72 (26%) were positive for adenovirus and 13 (5%) for influenza A. In non-recruit units the proportion positive for adenovirus was much lower. Of 379 pairs of serum from boy entrants, 12 (3%) were positive for adenovirus and 15 (4%) for influenza A. Of 1,015 pairs from patients in operational units, 44 (4%) were positive for adenovirus and 146 (14%) for influenza A, and one was positive for both; in addition two patients showed a rising titre against influenza virus B, and five against Sendai virus. Fifty-two adenovirus strains were isolated, all but one from recruits; 35 of these were typed, and all belonged to type 7. The time distribution of the main serological results is shown in Fig. 2.

These findings probably give a reasonable indication of the relative frequency of adenovirus and influenza A infections in the three types of unit. But the considerable differences in the incidence of respiratory illness shown in Fig. 1 must influence any estimates of illness attack rates due to these agents. The proportion of illness due to influenza A was lower in recruits than in non-recruits, but the attack rate due to this virus must have been almost twice as high. By the same argument the influenza A attack rate in non-recruits was probably very little higher than in boy entrants. The adenovirus experience was quite different, both the proportion of illness and attack rates being much higher in recruits. During the months of February, March, and April, when monthly respiratory admission rates in recruit units approached 10%, over half the paired sera tested were positive for adenovirus. On the other hand, the incidence of illness due to adenovirus among non-recruits and boy entrants was low.

FIG. 1.—Respiratory illness admission rates, 1955-7.

FIG. 2.—Serological results, 1955-7.

Excluding recruits, the age of patients with adenovirus infection tended to be lower than that of those with influenza A. Only 3 (5%) of the 56 positive for adenovirus were over 25 years of age, and two of these were medical officers; 28% of those with influenza A were over this age.

1956-7.—The most notable feature of the results obtained during this winter was the almost complete absence of adenovirus infection in the recruit units. From 1,110 throat swabs tested in HeLa cells only four strains were isolated—three of type 3 and one of type 4. The only other evidence of adenovirus infection was at a station for boy entrants where four strains—two of type 4 and two of type 7—were isolated during a small outbreak of respiratory illness at the end of March. Influenza A, on the other hand, was responsible for several outbreaks investigated at non-recruit and boys' units during February, March, and April, and in March it accounted for about half the cases with physical or x-ray changes in the chest at the recruit unit where paired sera from such patients were collected as a routine.

Clinical Observations

The symptoms and signs of acute respiratory illnesses due to a single agent vary considerably, and this tends to obscure differences between illnesses caused by one agent and those caused by another. No great diagnostic accuracy in the individual case can therefore be expected from clinical examination alone. Some differences were apparent, however, in the frequency of certain symptoms and signs between groups of patients with adenovirus infection, influenza A, and other acute respiratory illnesses—almost all of unknown aetiology. This may be seen in the Table, which

Clinical Findings and Serological Results on Non-recruit Units, 1955-6

	Influenza A	Adenovirus Infection	Remainder*
No. illnesses	161	56	1,177
No. with adequate record	161	56	1,140
Symptoms present (%):			
Headache	82	71	75
Sweating	57	64	47
Shivering	61	57	43
Muscular pains	54	25	32
Sore throat	63	89	72
Cough	80	59	45
Nasal symptoms	48	37	41
Diarrhoea	1	2	2
Vomiting	9	5	6
Conjunctivitis	20	11	8
Fever:			
102° F. (38.9° C.) or more	28%	18%	16%
Average duration	2.6 days	3.1 days	2.1 days

* All serologically negative except two patients with a rising titre to influenza virus B, five to Sendai virus, and one to both adenovirus and influenza virus A.

summarizes the clinical records of non-recruits during the 1955-6 survey. Cough, muscular pains, and a temperature of 102° F. (38.9° C.) or more were rather more frequent in those with influenza, and sore throat in those with adenovirus infection. It is interesting that conjunctivitis was more frequent in those with influenza, but it is doubtful whether the conjunctivitis seen in Service men during the winter months was of the same type as that noted in schoolchildren during summer outbreaks of pharyngo-conjunctival fever (Kendall *et al.*, 1957).

Invaliding

In the years 1953 and 1954, 195 men and women were invalided from the R.A.F. because of disease of the respiratory tract other than tuberculosis or cancer, and a disability pension was awarded to most of them. At least 90% of these were discharged because of bronchitis, bronchiectasis, pneumonia, pulmonary fibrosis, or empyema. More than 40% served less than six months, and all of these had suffered as recruits from an acute respiratory illness from which they did not fully recover and which led directly to invaliding. A further 14% who had served less than one year had mostly been ill as recruits and spent almost the

entire period of their service in hospital. Recurrent respiratory disease played little part in the causes of invaliding; two-thirds suffered from only one illness during their service. A history of pneumonia or bronchitis before entry into the R.A.F. was recorded in 44% of those invalided with less than six months' service, but it is hard to know what importance to give to this observation.

The acute illness that led to invaliding was usually in the winter or early spring, during those months when the incidence of respiratory diseases is highest at recruit stations. About one in every 250 acute respiratory admissions at a recruit station led to invaliding before the completion of six months' service. This amounts to the permanent loss of perhaps one in every 1,000 airmen recruited during the first quarter of the year.

Discussion

Acute respiratory disease in military personnel is a serious problem. Not only is time lost during training but a substantial number are invalided with serious lung damage before any useful service has been performed. Among air crew respiratory infections have special importance because of pressure effects on the middle ear at high altitudes. In the Royal Air Force, the incidence of acute respiratory disease is highest by far in the recruit units. This is not an isolated finding, and has been reported not only in the United States of America but also in Switzerland (Löffler *et al.*, 1956) and Holland (van der Veen and Kok, 1957). The major cause of respiratory diseases invaliding in the R.A.F. is illness acquired at recruit camps. Time spent at these stations represents at most one-twelfth of the total service, whereas approximately two-thirds of all illness leading to this type of medical discharge is acquired during this period.

The adenoviruses and influenza viruses may well account for at least half the illnesses during the severe and protracted winter epidemics in recruit stations. In non-recruit units, as in the adult civilian population, the adenoviruses do not appear to be a frequent cause of illness; though most outbreaks were due to influenza virus, the cause of a relatively high proportion of acute respiratory disease requiring admission to sick-quarters remains unknown. Adenovirus infection may only be able to spread readily under the exceptional conditions of a recruit camp with its large and rapidly changing population of young men drawn from all parts of the country and introduced to residential community life for the first time. Apart from some radical change in recruit reception and training, effective vaccines, used if possible before arrival at the recruit units, would appear to offer the best hope of reducing the problem. Much can already be expected from influenza A vaccines, and field trials in the United States have shown that adenovirus vaccines are capable of affording a high degree of protection against viruses of the same type (Bell *et al.*, 1956; Stallones *et al.*, 1957).

Summary

In surveys of acute respiratory illness in selected R.A.F. stations in 1955-7 it was found that the incidence of sickness requiring admission to sick-quarters was far higher in recruit units than in operational stations.

Adenovirus infection was probably responsible for at least half the respiratory disease admissions in recruit units during the periods of highest prevalence in 1956, but was completely absent from the same units in 1957; it was responsible for very few admissions in other types of unit.

Influenza virus A was an important cause of illness among recruits in both winters, and accounted for at least 12% of respiratory admissions in other units in 1955-6 and for outbreaks at several stations in 1956-7.

More than half those invalided from the R.A.F. in 1953 or 1954 with a respiratory disease, other than

tuberculosis or cancer, were discharged as a result of an acute respiratory illness contracted during their recruit training.

We are indebted to the P.M.O. Technical Training Command, R.A.F., and other medical officers for granting us facilities to conduct these studies; to many station medical officers and in particular to Wing Commander M. Robertson, Wing Commander M. O. Richardson, and Squadron Leader W. G. Cooke for their co-operation in taking blood samples and completing the special records required; to Wing Commander R. J. A. Morris for help with records of invaliding; to Sergeant A. T. Coukham for valuable technical assistance; and to Dr. P. S. Gardner and Dr. G. B. Bruce White, of the Public Health Laboratory Service, for help with special laboratory tests.

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DINITROPHENOL AND DIABETES MELLITUS

A COMPARISON WITH SALICYLATE

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Salicylate and 2:4-dinitrophenol (D.N.P.) both inhibit oxidative phosphorylation (Loomis and Lipmann, 1948; Brody, 1956). Salicylate also controls the clinical and biochemical abnormalities in moderately severe diabetes mellitus (Reid, Macdougall, and Andrews, 1957). The question that arises is whether D.N.P. has a similar action in this disease.

D.N.P., a powerful metabolic stimulant, was grossly misused in the 1930's as a slimming agent. The principles for prolonged use of a dye substance in clinical medicine put forward by Shannon *et al.* (1944) were not fully appreciated, and the high incidence of serious toxic effects from prolonged administration led to its withdrawal as a therapeutic agent. Since then it has been used only occasionally in clinical practice, although it is still extensively employed in biological investigations.

A short, carefully controlled trial of D.N.P. in diabetes mellitus has been carried out to discover its effect on blood sugar, glycosuria, and glucose tolerance. Six elderly ladies with mild to moderately severe diabetes were investigated along the lines previously described in the aspirin trial. They were given a constant low carbohydrate diet (150 g.) for at least 10 days before starting D.N.P., to establish the effect of diet alone, and the same diet was maintained throughout the whole investigation.

D.N.P. was given for 14 days in doses of 100–300 mg. in capsules daily, actual doses being controlled by

repeated plasma drug levels (Parker, 1949) and by measurement of oxygen consumption of fasting, resting patients with a Benedict–Roth machine to calculate the basal metabolic rate (B.M.R.) (Robertson and Reid, 1952). An attempt was made to induce the same order of metabolic stimulation with D.N.P. as was previously induced in diabetics successfully treated with aspirin. The effects of D.N.P. on fasting blood sugar estimated by Lehmann and Silk's (1952) modification of Folin and Wu's method, on glycosuria determined by Benedict's (1911) method, and on oral glucose tolerance were examined. Since none of the patients had abnormal quantities of ketones in the urine, quantitative measurement was not undertaken.

Results

Dose of D.N.P., Plasma Level, and B.M.R.—Frequent determinations of plasma D.N.P. level and oxygen consumption were necessary to control therapy and to avoid

TABLE I.—Dose and Plasma D.N.P.

Day	Plasma D.N.P. (mg./litre)					
	Case 1 55 yrs. (5)*	Case 2 55 yrs. (52)	Case 3 57 yrs. (2)	Case 4 59 yrs. (96)	Case 5 60 yrs. (12)	Case 6 76 yrs. (12)
1	—	—	21	24	—	15
2	45	40	47	31	40	30
3	45	40	47	31	40	30
4	46	—	54	29	43	44
5	45	—	54	38	41	43
6	49	33	47	—	—	—
7	—	—	—	32	36	32
8	57	36	38	38	45	15
9	—	—	47	43	—	—
10	49	33	42	34	39	48
11	—	48	—	38	—	—
12	45	—	52	40	37	46
13	—	43	—	—	—	—
14	40	50	48	35	41	39
Mean (2–14 days)	47	40	48	35	40	34
Total dose (g.)	2.8	3.1	2.25	3.5	2.9	3.05
Maintenance dose (mg. daily)	150–200	200–300	100–200	200–300	200–300	150–300

* Duration of diabetes in months.

undesirable reactions. Table I gives relevant clinical particulars as well as doses and plasma levels of D.N.P. A fairly steady plasma concentration of D.N.P. was reached in each patient after the first day's dosage; the mean values of the six patients between the second and fourteenth days ranged from 34 to 48 mg./litre. The relation between plasma D.N.P. and the B.M.R. is shown in Fig. 1:

an obvious and expected rise in B.M.R. accompanied an increase in plasma D.N.P. concentration. The regression line and its 95% confidence limits are shown. No toxic effects from D.N.P. were encountered, and the results, in addition to defining a significant relation between plasma D.N.P. and B.M.R., indicate that the same order of metabolic

FIG. 1.—Relation between the rise in B.M.R. from D.N.P. and the plasma concentration of the drug in six female diabetics. The regression line and its 95% confidence limits are shown. The coefficient of correlation, r , was 0.54 with $p > 0.01$, but < 0.001 ($t_{0.05} \times \sigma r = 26.5$).