A SURVEY OF THYROID ENLARGEMENT IN TWO GENERAL PRACTICES IN GREAT BRITAIN

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The difficulties inherent in examining a large sample of the population for thyroid enlargement have restricted previous investigations in the United Kingdom. Usually schoolchildren have been examined, as they are easily accessible and their health is a subject of concern of the education authorities. These surveys are of limited value, as simple goitre commonly develops after school-leaving age, and the incidence of thyroid enlargement in schoolchildren may not be an indication of the prevalence among the later age-groups. Murray *et al.* (1948) attempted to survey the population of the village of Hook Norton, in Oxfordshire, but only 50% were examined and no description of their selection procedure was given. The geographical incidence of thyroid enlargement is of importance in investigating its aetiology, and unbiased surveys of the population at risk are necessary for comparisons of different regions.

It was decided to attempt an investigation of this type by examining the patients in two general practices. In Sheffield the practice is mainly in the Crosspool district, on the hilly outskirts on the west side of the city and close to the Derbyshire border. It is a widespread impression that simple goitre is a common condition in Sheffield and surrounding regions, especially in Derbyshire. For comparison the other survey was carried out in a practice in Scotland, as simple goitre has always been uncommon there. As the practice in Ormiston includes patients living in the town and also in the surrounding rural area, the survey was confined to those patients living within the parish of Ormiston, the practice in Sheffield being entirely suburban.

Classification

Many surveys of thyroid enlargement have been vague in defining enlargement. Murray *et al.* (1948) used visibility as the main criterion in distinguishing degrees of enlargement. Their initial abnormal stage is described as visible to the trained observer, and the description suggests that this includes any deviation from the normal contour of the neck seen at rest or on swallowing. They are not precise about patients in whom there was any doubt about a swelling in the region of the thyroid. This classification was also used by Hughes *et al.* (1959), and they reported a 40% incidence of thyroid enlargement in children in Oxfordshire schools. We feel that this method magnifies the incidence of goitre, and prefer to classify as "invisible" whenever the observer is in any doubt.

Pérez *et al.* (1960) also stated that doubtful cases of enlarged glands should be classified as normal, but their classification, which includes invisible glands enlarged only to palpation, has two incompatible statements. On the one hand they accept a gland as goitrous only when it is four to five times the normal volume. It is generally accepted that the weight of the normal thyroid gland in the adult is between 15 and 25 g. (De Smet, 1960). On the other hand they state that any thyroid gland whose lobes are greater than the terminal phalanges of the thumbs of the subject being examined should be considered goitrous. As the average volume of the two distal phalanges in adults is approximately 20 ml. these two statements are not reconcilable.

The classification used in the present surveys has been developed from studies on thyroid glands removed surgically and at necropsy (Table I). For ease of description a goitre is regarded as a thyroid gland showing stage 2 or 3 enlargement.

TABLE I.—Classification of Degree of Thyroid Enlargement

	On Inspection	On Palpation
Stage 0	Not visible	Not palpable
Stage 1	Not visible	Palpable but less than 40 g.
Stage 2	Visible	Palpable but less than 40 g.
Stage 3	Visible	Palpable and more than 40 g.

The method of examination consisted in inspection of the neck in a good light, and a decision was then taken concerning visibility of the thyroid. The neck was then palpated from behind, when a visible swelling was confirmed to be thyroid in origin, and the size of the gland was decided. Consistency, asymmetry, and presence of nodules were noted and the size was classified as under 40 g. and in 20-g. steps above 40 g. General nutritional status was also noted. An arbitrary value of 40 g. has been used in deciding between stage 2 and stage 3 enlargement, as this is approximately twice the size of the normal adult gland and many visible glands are found to be under 40 g. in weight. Thyroid glands in the normal position and larger than 40 g. are always visible and usually obvious at a glance. Glands which are palpable, but invisible, are generally under 40 g. This is not always true, depending on the shape and thickness of the neck, but we have found that visible glands are usually bigger than glands enlarged only on palpation. Illustrations of the visible stages are shown in Figs. 1 and 2.

Uniformity of classification was achieved by all the observers, who examined many hospital patients before the surveys were begun. It should be emphasized that whenever there was doubt about the degree of enlargement the lesser degree was recorded. The results were recorded on prepared cards along with details of previous residence and personal history of thyroid disease.

Incidence of Thyroid Enlargement

A valid comparison depends on the completeness of the examination in each district. This was achieved within the limits of practicability, in that 98% of all the people in each group were examined. This often necessitated several visits to contact elusive individuals.

The age and sex distribution of patients examined in Ormiston and Sheffield are shown in Fig. 3. Clearly the two practices are not similar. There are many more elderly women in the Sheffield practice, and this is probably associated with its being in the care of female

practitioners. In Ormiston the sex ratio is almost unity and the age distribution is similar for both sexes. In Sheffield the age distribution of males is like that for both sexes in Ormiston. The excess of old women in Sheffield was anticipated, and provided a favourable opportunity for studying the familial incidence of goitre.

The total number of patients with thyroid enlargement in the two districts and the distribution by age and sex are shown in Table II. The percentage incidence of visible thyroid enlargement (stages 2 and 3) is shown in Fig. 4. Thyroid enlargement clearly occurs much more frequently in Sheffield and this is seen in both men and women. The age distribution of the incidence of goitre (stages 2 and 3 enlargement) is also strikingly different in the two districts. In Sheffield the peak incidence is in

the age-group 20-29 years and the condition is most prevalent between 10 and 49 years (Table III). For both sexes the rate at 10-49 years is significantly greater than that for the group 50 years and above (males $\chi^2=21.9$, $P<0.001$; females $\chi^2=32.2$, $P<0.001$). In Ormiston, on the other hand, among females the rates at 10-49 years and 50 years and above were not significantly different ($\chi^2=0.44$, $P>0.5$), and indeed give no suggestion that the prevalence was less in older women; among men the prevalence was so low as to give no indication of any age pattern. In both districts goitre is commoner in women, but the difference between the sexes is less marked in Sheffield. The overall female/male sex ratio for the percentage incidence of goitre is about 2:1 in Sheffield and 14:1 in Ormiston.

FIG. 1.—Stage 2 thyroid enlargement. The gland is visible but judged to be under 40 g. in weight.

FIG. 2.—Stage 3 thyroid enlargement. The gland is obvious and judged to be more than 40 g. in weight.

Observer Variation in the Surveys

When about 75% of the patients had been examined by the general practitioners, 105 patients in Sheffield

FIG. 3.—Age and sex distribution in the groups surveyed in Ormiston and Sheffield.

TABLE II.—Incidence of Thyroid Enlargement in Ormiston and Sheffield

Age-group	No of Patients Examined in				Stage 1 No. of Patients whose Thyroid was Palpable but Less than 40 g. and was not Visible				Stage 2 No. of Patients whose Thyroid was Palpable but Less than 40 g. and was Visible				Stage 3 No. of Patients whose Thyroid was More than 40 g. on Palpation and was Visible			
	Ormiston		Sheffield		Ormiston		Sheffield		Ormiston		Sheffield		Ormiston		Sheffield	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
0-9	101	98	154	146	2	1	62	57	0	0	14	18	0	0	0	0
10-19	126	150	162	186	10	19	91	87	0	3	27	67	0	4	4	5
20-29	84	83	57	130	6	8	26	49	0	1	19	54	0	3	2	1
30-39	97	102	77	177	7	8	47	72	0	1	9	62	0	4	0	9
40-49	120	118	107	218	9	17	60	95	1	1	10	60	0	3	0	12
50-59	86	72	100	238	1	7	54	117	0	3	1	40	0	1	0	2
60-69	51	59	49	186	1	7	21	82	0	2	2	18	0	2	1	4
70+	30	42	48	221	2	4	13	80	1	2	1	20	0	1	1	18
Total	695	724	754	1,502	38	71	374	639	2	13	83	339	0	18	8	51
%	(49.0)	(51.0)	(33.5)	(66.5)	(5.5)	(9.8)	(49.6)	(42.6)	(0.3)	(1.8)	(11.0)	(22.6)	(0.0)	(2.4)	(1.1)	(3.4)
Grand total	1,419		2,256		109		1,013		15		422		18		59	

and 98 patients in Ormiston were examined by another observer (R. K.). This second examination was done independently and without knowledge of the result of the previous examination, and the patients were unselected, apart from the selection involved in whether they were at home or not when the visit was made.

The results are shown in Tables IV and V. Manifestly there was more variation between observers in Sheffield. This is possibly due to the much higher incidence of thyroid enlargement in Sheffield, and it seems reasonable to expect more differences to arise in classifying these mildly enlarged glands in comparison with a region where the great majority are impalpable. In the comparisons there was agreement in 76% of cases in Sheffield and in 96% in Ormiston. In Sheffield there was disagreement in 14% of patients with respect to

glands palpable or impalpable, and in 7% between non-visible and visible glands. There was disagreement by more than one stage in only 4% of patients. The corresponding results in Ormiston were 3% and 1%, with no disagreement by more than one stage. In Sheffield the incidence of visible thyroid enlargement recorded by the practitioners (M. R. or E. W.) was 22% and 19% by the second observer (R. K.). In Ormiston these results were 3% (J. S. M.) and 4% (R. K.). The fact that these incidences are not significantly different from those found in the complete practices is good evidence that the groups examined for observer variation were unbiased. The second observer (R. K.) recorded a slightly smaller incidence of thyroid enlargement in Sheffield. It seems reasonable to conclude that the standards for thyroid enlargement had not changed significantly from the beginning of the surveys, and that it is extremely improbable that observer error could account for the widely differing incidences of thyroid enlargement in the two places.

Incidence of Thyroid Disease and Treatment

Some very striking differences are seen when the findings derived from the personal histories of the patients are compared (Table VI). The difference between the two places is over fivefold for a history of goitre in adolescence. A diagnosis of thyrotoxicosis, past or present, was accepted only if there was adequate confirmation of the diagnosis by investigation

TABLE VI.—History of Incidence of Thyroid Disorders and of Treatment for Thyroid Disorders at Ormiston and Sheffield

	Ormiston			Sheffield		
	M	F	Total	M	F	Total
Total	695	724	1,419	754	1,502	2,256
Previous adolescent goitre ..	0	9	9	4	47	51*
Thyrotoxicosis	1	0	1	1	16	17*
Thyroid operations	2	4	6	0	17	17
Antithyroid drugs	1	0	1	0	9	9
¹³¹ I therapy	0	0	0	0	3	3
Oral iodine	0	0	3	3	14	17†
Thyroid or thyroxine therapy ..	0	2	2	2	7	9

* $P < 0.01$. † $0.05 > P > 0.01$.

FIG. 4.—Incidence of goitre (stages 2 and 3 thyroid enlargement) in Ormiston and Sheffield.

TABLE III.—Percentage of Different Age-groups with Goitre (Stages 2 and 3 Combined)

Age	Ormiston		Sheffield	
	M	F	M	F
0-9	0	0	9	12.3
10-49	0.2	4.4	17.6	38.0
50+	0.6	6.4	3.0	15.0

TABLE IV.—Observer Variation in 98 Patients in Ormiston

Degree of Thyroid Enlargement Found by J.S.M.	Degree of Thyroid Enlargement Found by R.K.			
	Stage 0	Stage 1	Stage 2	Stage 3
Stage 0	83	2	0	0
Stage 1	1	8	1	0
Stage 2	0	0	2	0
Stage 3	0	0	0	1

TABLE V.—Observer Variation in 105 Patients in Sheffield

Degree of Thyroid Enlargement Found by M.R. and E.W.	Degree of Thyroid Enlargement Found by R.K.			
	Stage 0	Stage 1	Stage 2	Stage 3
Stage 0	30	6	2	0
Stage 1	9	34	1	0
Stage 2	3	3	16	0
Stage 3	0	0	1	0

in hospital and followed by medical or surgical treatment. All the cases of thyrotoxicosis were already known to the practitioners. It is impressive that there was only one case in Ormiston, compared with 17 in Sheffield. The incidence of a history of treatment for thyroid disorder is consistently higher in Sheffield.

Incidence of Goitre in Relatives

In Sheffield, where goitre is prevalent, the frequency of thyroid enlargement in close female relatives has been assessed, as many mothers, daughters, and sisters were included in the practice.

The incidence in mothers and daughters over 10 years of age is shown in Table VII. Though goitrous mothers had a higher proportion of goitrous daughters than the unaffected mothers this difference does not attain

TABLE VII.—Incidence of Goitre in Mothers and Daughters in Sheffield

Mother		Daughters over 10 Years	
Goitre	54	Goitre	31 (44.9%)
No goitre	192	No goitre	38 (34.4%)
		Goitre	77 (34.4%)
		No goitre	147
		$\chi^2 = 2.52$	$0.2 > P > 0.1$

statistical significance. Many of the mothers were elderly, and consideration of the distribution of goitre by age in Sheffield women shown in Fig. 4 suggests that many of these older mothers might have had a goitre when younger which subsequently disappeared. A further analysis was accordingly restricted to mothers and daughters in the age range of 10 to 49 years when the incidence of goitre is high. The differences become greater (Table VIII) but still are not significant at the 5% level.

TABLE VIII.—Incidence of Goitre in Mothers and Daughters in Sheffield, Both in Range 10-49 Years

Mother		Daughters	
Goitre	 33	Goitre	 20 (46.5%)
No goitre	 81	No goitre	 23
		Goitre	 33 (31.7%)
		No goitre	 71
		$\chi^2=2.882$ 0.1>P>0.05	

A contrast is seen in the incidence of goitre in sisters (Table IX). Taking the youngest sister over 10 years of age, a significantly higher incidence of goitre was found in her elder sisters if she herself was goitrous.

TABLE IX.—Incidence of Goitre in Sisters in Sheffield

Younger Sister over 10 Years		Older Sisters	
Goitre	 26	Goitre	 16 (50.0%)
No goitre	 76	No goitre	 16
		Goitre	 21 (27.6%)
		No goitre	 65
		$\chi^2=7.091$ 0.01>P>0.001	

Effect of Duration of Residence in Sheffield

Many of the women had lived all their lives in Sheffield. Some had spent at least the first 20 years of life in an area outside Sheffield and the immediately surrounding counties of Yorkshire and Derbyshire but had subsequently come to Sheffield. The incidence of goitre has been examined in these two groups (Table X). In those aged 20-49 years the incidence of goitre is greater in the Sheffield born and bred women than in the immigrants, but the difference does not quite attain

TABLE X.—Incidence of Goitre in Women Living all Life in Sheffield and in Women Coming to Sheffield from Outside Yorkshire and Derbyshire After 20 Years of Age

	All Life in Sheffield		Coming after 20 Years of Age	
Women 20-49 years	Goitre	.. 125 (39.4%)	Goitre	.. 29 (29.9%)
	No goitre	.. 192	No goitre	.. 68
			$\chi^2=2.890$ 0.1>P>0.05	
Women 50+ years	Goitre	.. 52 (13.8%)	Goitre	.. 14 (11.9%)
	No goitre	.. 325	No goitre	.. 104
			$\chi^2=0.289$ 0.7>P>0.5	
Total	Goitre	.. 177 (25.5%)	Goitre	.. 43 (20.0%)
	No goitre	.. 517	No goitre	.. 172
			$\chi^2=2.711$ 0.1>P>0.05	

statistical significance. Only two women at the time of examination had come to Sheffield within the previous six months and only five more within the previous year. The majority of the women who had come to Sheffield had already been resident there for many years when the survey was carried out. In the women over 50 years no difference is apparent between the two groups, but the overwhelming majority of the immigrants to Sheffield in this age-group had lived there for 30 years or more.

Effect of Child-bearing

The incidence of goitre in single women, married women without children, and married women with

children is shown in Table XI. Child-bearing clearly does not increase the incidence of goitre.

TABLE XI.—Incidence of Goitre in Single Women and in Married Women Without and With Children

Age		Goitre	No Goitre
20-49 years	Single	43 (39.5%)	66
	Married, no children	44 (48.4%)	47
	Married, with children	116 (35.7%)	209
		$\chi^2=4.840$ 0.1>P>0.05	
50+ years	Single	27 (16.8%)	134
	Married, no children	14 (13.5%)	90
	Married, with children	53 (14.0%)	326
		$\chi^2=0.832$ 0.7>P>0.5	

Discussion

All goitre surveys are bedevilled by the difficulty in achieving a uniform classification of thyroid enlargement, and comparative incidences of goitre reported by different observers have had little meaning. The main difficulty has been in deciding the degree of enlargement that is certainly abnormal. This in turn depends on the size of the normal thyroid gland. On the basis of necropsy studies, Kloepfel (1910) found the thyroid gland in the adult Central European to weigh 34-41 g., whereas Marine (1922) reported that the ratio of thyroid weight to body weight was less than 0.35 g./kg. Thus a man weighing 70 kg. had a thyroid gland weighing 24.5 g. Aschoff (1924) studied the relationship of thyroid weight to age and found the maximal weight to be 25 g. The normal thyroid gland was found to be between 20 and 25 g. by many other workers (Jaffe, 1930; Olesen, 1926, 1929; Rice, 1931; McClendon and Williams, 1932). McCarrison (1935) confirmed the constant ratio to body weight found by Marine (1922), but claimed that this ratio increased temporarily at puberty.

In the Belgian Congo, De Smet (1960) measured normal thyroid weights and found a range of 20-25 g. in adults. In Iceland, Sigurjonsson (1961) found the normal thyroid weight to be 14 g. in men and less in women, this being a region where iodine intake is probably high. Clearly the normal thyroid weight is usually 20-25 g., and may be less than this in certain regions. Hazard and Kaufman (1952) considered that any gland over 35 g. was abnormal. This same arbitrary weight was used by Hull (1955), and in Colorado he found 21.3% of thyroid glands to be greater than this weight. Many arbitrary standards of abnormality have been used, when only the results of clinical examination have been available. Murray *et al.* (1948) accepted visibility as the criterion for abnormality, as did the Study Group on Endemic Goitre of the World Health Organization, but the former group accepted as abnormal any gland which could be seen, whereas the latter accepted as goitrous only a thyroid gland which was obviously visible and, judging from their illustration, probably weighed about 60-80 g. Accordingly the results of surveys by these two groups cannot be compared.

In the present study all palpable and visible glands were recorded. The definition of normal and abnormal has been avoided, but clearly the majority of glands cannot be palpated or seen. As the normal gland is about 20-25 g. it is reasonable to assume that palpable glands are heavier than this. A visible gland is usually larger still, and if diffusely enlarged a gland becomes visible at about 35-40 g. in an average neck. Thyroids

less than this weight with localized enlargements may be visible. It is unlikely that survey results can be compared whenever arbitrary divisions between normality and abnormality are used.

Geographical differences found by the same observers are much more valid than those between different surveys. In 1838, Inglis noted striking differences in incidence of goitre in different parts of England, and a very low incidence in Scotland. This was confirmed by Roberts (1882), and later a detailed account was given by Berry (1901). In 1924 all schoolchildren aged 12 years in England were examined at the request of the Board of Education and the results were published by Campbell (1927) and in more detail by Stocks (1928). Unfortunately this survey has doubtful significance, as no standards for examination were given to the school medical officers. The resulting observer-variation was checked by Stocks (1928) and found to be very large. Sheffield was reported as an area of moderate prevalence of goitre, with an incidence of 4.5% in girls. This large survey confirmed that sex ratio for goitre always approached unity in all areas with a high prevalence of goitre. Striking differences in goitre incidences in girls in Somerset and Suffolk were recorded by Young *et al.* (1936), using a similar classification to that used in the present study and to that of Pérez *et al.* (1960). In Somerset 56% of children between 6 and 14 years had visible thyroid enlargement; in Suffolk it was only 3.7%. Davies and Rogers (1940) noted a high incidence of goitre in adult women in South Wales, and Lisney (1951) found thyroid enlargement in 15.6% of a group of pregnant women in Dorset.

The first attempt to survey the population of one village in Oxfordshire was reported by Murray *et al.* (1948), but only 50% of the inhabitants were examined, and an incidence of visible enlargement of 26% was recorded. Selected groups of adult women from other regions in England were examined by these workers, and incidences varying from 9% to 50% were found. They also examined schoolchildren from many regions in both England and Scotland and found much higher incidences in England, especially in Oxfordshire and Dorsetshire. Hughes *et al.* (1959) reported the incidences of goitre found in schoolchildren more than 10 years after the same schools had been surveyed by Murray *et al.* (1948) and showed that no decrease had occurred.

The present results from Sheffield and Ormiston confirm that striking regional differences in thyroid enlargement still occur, but it is not possible to compare the incidences with those previously reported from various parts of England and Scotland, for the reasons already given. The decrease in sex ratio from 14:1 in Ormiston to 2:1 in Sheffield also confirms previous observations. The magnitude of observer variation, though it cannot account for the regional differences, indicates that the observed incidences are only approximations. The increased prevalence of goitre in Sheffield is associated with a higher incidence of other thyroid disorders, and the increased number of thyroidectomies is also an indication of this. It is possible that this difference might be due to selection for surgical treatment, but it appears from studying the cases that operation is recommended more often in the low goitre area because of the possibility that the enlargement may be carcinomatous. The very striking difference in incidence of thyrotoxicosis is of great interest, and seems entirely unequivocal. Campbell (1927), using death rates for thyrotoxicosis, showed an association between

incidence of this condition and simple goitre in England and Wales. Similar correlations have been reported from North and South America by McClendon and Williams (1932) and Perinetti (1952), from Finland by Saxen and Saxen (1954), and from Australia by Wyndham (1940) and Clements (1954). No association between these conditions has been reported from Switzerland or the Himalayas, where goitre was prevalent. Direct evidence for such an association is given in the present work, but no causal relationship can be assumed.

The reason for the conspicuous difference in thyroid size in the two districts remains to be determined. The iodide content of the water in both places is similar, about 1 µg./l., but it is clear that the supply of iodide must be obtained from food rather than water. Dietetic differences may exist, and these are at present being investigated. Considerable goitrogenic activity can be detected in the Sheffield milk during the spring months by experiments on rats (Kilpatrick *et al.*, 1961), but the relevance of this finding to human goitre is unknown.

There has recently been much interest in congenital goitre, and the various biochemical abnormalities found in this condition seem to be genetically determined (Stanbury *et al.*, 1956a, 1956b; McGirr *et al.*, 1959; McGirr, 1960). The evidence for a familial association of simple goitre not congenital in type is much less strong. It has usually been assumed to occur (Greer, 1955), but it is difficult to distinguish between heredity and environment. The findings in the mothers and daughters and in the sisters, and in those who having spent their childhood elsewhere came to Sheffield in later life, suggest strongly that the prevalence of goitre is due predominantly to an environmental factor.

Summary

A survey of the prevalence of thyroid enlargement has been carried out in two general practices, one in Ormiston, East Lothian, Scotland, and the other in Sheffield, England.

It was much commoner in Sheffield, where in men 12% and in women 25% of thyroid glands were visible. The corresponding figures in Ormiston were 0.3% and 4.3%. In Sheffield thyroid enlargement was most prevalent between 10 and 49 years of age and declined after 50 years of age in both sexes. In Ormiston the low incidence rose gradually with increasing age.

Examination of sisters, mothers, and daughters revealed some evidence of a familial incidence of goitre. Child-bearing did not increase the incidence.

The prevalence of goitre was not significantly less in women who had spent the first 20 years of life outside the district but had subsequently lived several years in Sheffield.

The incidence of thyrotoxicosis and of a history of treatment for thyroid disorders was much greater in Sheffield than in Ormiston.

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Preliminary Communications

Some Attempts to Produce an Experimental Vaccine with Rhinoviruses

By the use of primary human kidney cells maintained in roller tubes at 33° C. and with a pH of about 7, viruses which produce a cytopathic effect can be isolated from some human subjects with colds (Tyrrell and Parsons, 1960). They resemble the enteroviruses in their size and density, but differ from them in some other physical properties (Dimmock and Tyrrell, 1962). They have been named rhinoviruses (Andrewes *et al.*, 1961) and have been grouped together with the enteroviruses in the picornavirus family by the International Nomenclature Committee (paper in press).

Rhinoviruses can be isolated from 20–30% of common colds (Tyrrell and Bynoe, 1961; Hamre and Procknow, 1961; Kendall *et al.*, 1962; Hilleman *et al.*, 1962; Johnson *et al.*, 1962). Some will grow only in human-embryo-kidney (H.E.K.) cultures or human-embryo-lung (H.E.L.) fibroblasts (H strains), while others will grow in monkey-kidney cells as well as in human-embryo cells (M strains). There are several different serological types of both M strains and H strains (Taylor-Robinson and Tyrrell, 1962a; Hilleman *et al.*, 1962), and specific antibody to these serotypes is produced in humans in response to infection (Tyrrell and Bynoe, 1961; Hamparian *et al.*, 1961). It has been found that volun-

teers with high levels of serum antibody against H.G.P. virus, an M strain, can rarely be infected with H.G.P. virus, while volunteers with low levels of serum antibody are usually susceptible to infection (Bynoe *et al.*, 1960).

We have attempted to produce high levels of serum antibody without producing symptoms of the common cold, using P.K. (Sal/1/56M), a strain serologically identical with H.G.P. (Tyrrell and Bynoe, 1961), and administering it by various routes.

MATERIALS AND METHODS

Virus.—The virus used was the P.K. strain isolated in 1956, and later passed seven or eight times in H.E.K. One batch of virus was given a seventh passage in H.E.L. fibroblasts. The virus showed adaptation to tissue cultures by giving a more rapid cytopathic effect in H.E.K. and monkey-kidney cultures than did the unpassed virus. A formalized E.C.H.O. 28 vaccine was used for comparative purposes. This was supplied by Dr. J. Holper, of Abbott Laboratories Ltd. E.C.H.O. 28 is similar to the M type rhinoviruses. The vaccine was given as two intramuscular injections of 1 ml. administered one week apart as recommended by the makers.

Tissue Cultures.—H.E.K. cell cultures were prepared as described earlier (Tyrrell *et al.*, 1960). They were washed three times before inoculation and maintained in medium 199, the pH of which was adjusted to about 7.2 by adding CO₂ in the gas phase. A human diploid fibroblast cell strain was prepared from embryo-lung tissue as described by Hayflick and Moorhead (1961), but using medium 199 instead of Eagle's medium. The cultures were maintained as described above.

Virus Pools.—Bottle or tube cultures were inoculated with virus and rolled at 33° C. until the cell sheet had completely degenerated. The medium was stored at –70° C. and tested for the presence of contaminating bacteria. The purity of the virus stock was shown by the fact that the virus was completely neutralized by antiserum against H.G.P. virus and no contaminating virus grew out in H.E.K. cells.

Virus Isolation and Neutralization Tests.—These were carried out in monkey-kidney-cell cultures as described earlier (Tyrrell and Parsons, 1960; Taylor-Robinson and Tyrrell, 1962b).

Volunteers.—Volunteers between the ages of 18 and 45 years were housed and observed as described by Andrewes (1948). Serum was collected on arrival at the unit, and a further specimen was collected by the volunteers' general practitioner two weeks after inoculation. In most cases nasal washings were taken daily from the second day after the virus was given until the fifth day. Faeces were collected from some volunteers. Control groups given normal tissue-culture fluid were included in all trials.

RESULTS

Inoculation of Volunteers with Live P.K. Virus by Different Routes.—P.K. virus grown in H.E.K. cultures was inoculated into groups of volunteers by one of three routes: each volunteer received 1 ml. of culture fluid as intranasal drops, or orally in 25 ml. of milk, or by intramuscular injection. The volunteers were observed for symptoms of the common cold, and attempts were made to isolate virus from the noses of volunteers inoculated intranasally and intramuscularly, and from the faeces of volunteers inoculated orally. The results