Further observations by us confirm and extend these findings. From the table it will be seen that most members of the androsterone-testosterone series cause

Substance	Total Amount given (mg.)	Effect on Vagina of Immature Rat	
		Normal	Ovariectomized
Androsterone	2	− (2)	
Androstanediol	2	+ (1)	
	4	+ (2)	− (1), + (1)
	5		+ (1)
Androstenedione	2	− (2)	
	2.5		− (1)
	3.0	− (1), + (1)	
trans-Dehydroandrosterone	2	+ (2)	− (1) + 1
	3		+ (1)
trans-Androstenediol	2	+ (2)	+ (1)
Methyl*trans*androstenediol	0.5	+ (2)	
	1.25		+ (1)
	1.5	+ (2)	
	2.0		+ (1)
Methylandrostanediol ...	0.5	+ (2)	
	1.25		− (1)
	1.6		+ (1)
3-Keto-17-methylandrostanol	0.6	+ (2)	− (2)
	1.24		+ (1)
Testosterone	0.125	− (1)	
	0.8	− (1)	
	2.0	− (1)	− (1)
	4.0	− (1)	
	6.0	+ (1)	
Methyltestosterone	0.4	− (1)	
	0.8	− (1)	− (1)
	2.0	− (1)	
	3.0	+ (1)	

Half of the total dose was given on two consecutive days to young female rats 30 to 40 grams weight. + means that the vagina became patent within six days, usually three to four days, after the first injection. Number of animals in each test is given in brackets. In all cases examined histologically opening of the vagina had been accompanied by cornification and by oestrous distension or enlargement of the uterus.

opening and cornification of the vagina and enlargement of the uterus of the immature rat—intact or ovariectomized—in doses comparable with those required to cause detectable growth of the prostate and seminal vesicles of the castrated male rat. The difference in oestrogenic activity between *trans*-dehydroandrosterone and its isomeride testosterone is remarkable. In view of the response of the ovariectomized animal, it is highly improbable that the oestrogenic action is exerted through some other endocrine organ (a similar effect is obtained on adrenalectomized ovariectomized rats, for instance), and the effect is presumably a direct one on the uterus and vagina. Whether or not transformation of the male hormone to oestrone or a similar substance takes place as a preliminary to its acting on the vagina and uterus, is impossible to say at this stage.

Oestrogenic Actions of the Male Hormones

We have also found that *trans*-dehydroandrosterone (1 mg. daily) will cause the appearance of female plumage in the Sebright bantam capon, an effect which can be produced by oestrone but not by androsterone.* (Callow and Parkes.[8])

In view of these results it seems likely that the oestrogenic action of testis and male urine extracts may be due, at least in part, to the presence of compounds exerting an oestrogenic action in addition to their primary male hormone action, rather than to the actual presence of oestrone or some other purely oestrogenic compound. The importance of this problem has been discussed by Parkes and Zuckerman,[14] and the isolation and identification of the oestrogenic substance or substances of human male urine, if other than *trans*-dehydroandrosterone, would appear to be a matter of pressing importance.

* The Sebright bantam cock is hen-feathered, male feathering appearing only after castration. On the basis of their experiment with androsterone and oestrone, Callow and Parkes[8] were inclined to believe that the hen-feathered condition of the normal male was due to the production of an oestrone-like substance by the testis, but in view of the above result it may equally well be due to the production of one or more of the oestrogenic male hormones.

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IMMUNIZATION BY THE ORAL ROUTE IN RESPIRATORY INFECTIONS

WITH SPECIAL REFERENCE TO INFLUENZA, COLDS, AND THEIR COMPLICATIONS

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Practicability of Oral Route for Vaccination Purposes

In recent years considerable interest has been aroused as to the possibility of utilizing the oral route for prophylactic immunization purposes not only against intestinal infections but against other general infections. There is now definite information on the value of the oral method in prophylactic typhoid immunization. The evidence, based on clinical and serological investigations on man, indicates that the oral method is just as efficient as the subcutaneous method, if not more so. Thus Hoffstadt and Thompson (1929)[1] have shown that agglutinins appear in the blood after three doses of a mixed typhoid and paratyphoid vaccine administered by the oral route on three successive days. They found that of ninety-three persons so treated 88.5 per cent. developed agglutinins for typhoid and a lesser number for paratyphoid bacilli as compared with 80 per cent. who, according to the literature, developed agglutinins after subcutaneous inoculation and 90 to 95 per cent. who show a positive Widal reaction after suffering from the disease. Pijper and Dau (1930)[2] have also confirmed from the results of their experiments the fact that the oral administration of typhoid vaccine produced agglutinins in man. These were found to be of the O (somatic) variety only. Krause-Shimkin (1931)[3] confirmed these results of Pijper and Dau. Ruge (1932)[4] has recorded a well-controlled experiment of oral vaccination compared with subcutaneous injection. The agglutinins against *B. typhosus* were actually higher in the orally vaccinated group after five

months than in the subcutaneously vaccinated series. Arnold (1933)[5] records results after the administration of bile and typhoid vaccine on three successive mornings. A group of sixty-one human beings showed agglutination in the serum after three weeks, the titre ranging from 1 in 40 to 1 in 320. All showed the presence of *B. typhosus* agglutinins.

Ross (1930, 1931, 1932),[6] in a series of experiments, has demonstrated successful immunization of rats against pneumococci by oral administration. These animals were protected against multiple lethal doses injected intraperitoneally. These experiments suggest the possibility of utilizing the oral method in immunizing human beings against pneumococcal infections.

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The Splanchnic Reaction

Lloyd Arnold (1933)[5] analyses some of the factors involved in peroral vaccination, and points out that the oral method of introducing a vaccine may be regarded from a new angle in the light of certain recent investigations. He calls attention to the investigations that have been made on the reactions of the splanchnic system to bacterial invasion, which we shall briefly summarize, as they have a practical bearing upon the problem of peroral vaccination. Petersen, Mueller, and Boikan (1927),[7] using an automatic pump, injected dilute suspensions of bacteria intravenously into dogs over long periods of time (six to twenty-four hours). In these experiments they were able to reproduce the clinical picture of the onset and course of an acute severe infectious process, and, by means of an analysis of the lymph, were able to follow some of the chemical changes coincident with the clinical changes. From these experiments the authors suggested that the reactions which supervene can be divided roughly into five periods—namely: (1) the latent period ; (2) the period of splanchnic stimulation ; (3) the period of fluctuations, with cellular efforts to restore the equilibrium ; (4) the period of maximum injury ; and (5) the pre-mortal period.

During the initial latent period the bacteria injected into the blood stream produced no demonstrable changes, and were immediately removed from the blood by the reticulo-endothelial system, largely in the liver. The fixation or phagocytosis of the living bacteria causes stimulation of the tissues. This initiates the second phase, which is characterized by stimulation. During this phase splanchnic vaso-dilatation and splanchnic leucocytosis take place, lymphorrhagia occurs, together with increased concentration of protein in the lymph, sugar mobilization, reduction in lymph coagulability, the appearance of soluble liver protein in the blood stream, and increased phagocytosis by the reticulo-endothelial system. After this period of stimulation the third phase makes its appearance, and so on.

Mueller and Petersen (1927)[8] demonstrated that the splanchnic system of the body—that is, the gastro-intestinal tract and its glandular appendages with their associated blood vessels and lymph channels—is stimulated by the injection of a foreign protein into the body, as well as after bacterial infections, and that this stimulation differs only in degree and is comparable to the pure physiological stimulation that occurs after the ingestion of food. Further, Nedzel and Arnold (1931)[9] and Fisher (1932)[10] have demonstrated that the intestinal mucosa is not an impermeable covering, and is permeable to bacteria. The bacteria then become fixed, phagocytosed, and disintegrated by intracellular ingestion within the reticulo-endothelial system in the splanchnic region. In other words, the splanchnic reticulo-endothelial system is the real barrier against a systemic invasion from the alimentary tract.

Lloyd Arnold (1933)[5] accordingly suggests that the ideal practical application of active immunization by the oral route would be to introduce a vaccine through the intestinal mucosa, and then stimulate the body sufficiently to produce a reaction similar to the stimulation phase described by Petersen, Mueller, and Boikan (1927),[7] but not of sufficient intensity to be compared to an inflammatory reaction.

Prevention of Colds, Influenza, and Respiratory Infections

So far very few reports are to be found in the literature of attempts to prevent colds, influenza, and respiratory infections by the administration of oral vaccines. Rockwell, Van Kirk, and Powell (1935),[11] however, have investigated the efficacy of an orally administered vaccine in reducing the incidence of the common cold over two winters. The vaccine they used was prepared as follows:

> Bacterial cultures were sterilized and the bacteria separated, absorbed in starch, dried, and finally placed in capsules. The organisms contained in each capsule were: pneumococci, 25 billions ; *Haemophilus influenzae*, 5 billions ; streptococci, 15 billions ; and *Micrococcus catarrhalis*, 5 billions. The capsules were administered on an empty stomach daily, with half a glass of cold water, for seven consecutive mornings, and thereafter once or twice a week during the season.

The effectiveness of the vaccine was judged by the average number of colds occurring in the vaccinated group when compared with their average during the preceding three years and with the average of " controls " not taking the vaccine. In the winter 1933–4 1,036 persons were included in the experiment, 500 being given the vaccine. In the succeeding winter 445 were given the vaccine and 469 others served as " controls." Comparing past experience with the experience of the experimental year, it was found that each treated group showed a larger decrease in the incidence of colds than its control group. Taking the statistics as a whole these groups had an average of 3.03 colds per person per year during the previous three years, while during the vaccine year their average was 1.3, a decrease of 57 per cent. The corresponding figures for the controls were 2.49 and 2.19, a decrease of 12 per cent. The essential decrease due to the vaccine is thus 45 per cent. in the first year. The statistics of the second year showed a decrease of 70 per cent. in the average number of colds in the vaccinated group as compared with a decrease of 26.3 per cent. in the control group. That is a comparable essential decrease of 43.7 per cent. in the second year.

Development of Specific Agglutinins to Pfeiffer's Bacillus

So far as we can ascertain from the literature no experiments have been recorded regarding the development of specific agglutinins to Pfeiffer's bacillus when vaccines of this organism are administered by mouth. In previous publications[12 13] we have shown that when Pfeiffer's bacillus is grown in bacterial symbiosis with *Anaeromyces bronchitica* in blood agar broth, not only is the growth and the virulence of Pfeiffer's bacillus thereby increased but a highly exalted toxin is also formed in the broth capable of producing, when injected into rabbits, a potent antiserum. This antiserum was shown to have a high agglutination titre, and contained complement-fixation bodies when tested against a Pfeiffer's bacillus antigen. Further, this antiserum was shown to have a definite neutralizing and protective effect in experimental animal infections with Pfeiffer's bacillus.

It occurred to us to try the effect of taking by mouth doses of this potent toxic vaccine with a view to ascertaining whether any specific immune bodies could be detected in the blood after oral administration, and

whether any toxic symptoms were produced. The vaccine was prepared as follows:

Five strains of Pfeiffer's bacillus along with a strain of *A. bronchitica* are grown together, in bacterial symbiosis, in blood agar broth flasks for seven days. At the end of this period the symbiotic broth culture is killed with 1 per cent. phenol overnight. It is then diluted with an equal amount of sterile saline so as to reduce the phenol content to 0.5 per cent. The vaccine is then tested for sterility.

One of us (E. T. T.) showed a slight trace of agglutinins in 1 in 10 dilution of his serum before oral administration. After four doses of 20 c.cm. of vaccine taken on an empty stomach every third day the agglutination titre of his serum rose to 1 in 80 complete agglutination and 1 in 160 partial agglutination. Six days later, after two further doses of 20 c.cm. the agglutination titre was found to have risen to 1 in 1,280. Having reached this high agglutination titre it was decided to ascertain the effect of a further dose of 20 c.cm. of oral vaccine, measuring the titre at shorter intervals.

Two days later the agglutination titre was					1 in 160
Four	,,	,,	,,	,,	1 in 2,560
Seven	,,	,,	,,	,,	1 in 5,120
Ten	,,	,,	,,	,,	1 in 2,560

It would thus appear that there is a definite tendency for the agglutination titre to drop during the first two days after oral administration, but that the agglutinins rapidly rise again on the fourth day and reach their maximum on the seventh day.

Subjective Symptoms after Oral Administration

One of us (R. T.) kept very careful notes of the toxic effects of the oral administration of such a vaccine. His serum was tested for agglutinins against a suspension of Pfeiffer's bacillus prior to oral administration, and showed no agglutinins in a dilution of 1 in 10. 20 c.cm. doses of oral vaccine were then taken on an empty stomach every two days until six doses (120 c.cm.) had been taken. Three days later, after completing six doses, the serum was tested for agglutinins. The serum showed definite agglutination in a dilution up to 1 in 80 and a trace in 1 in 160. The serum tested for complement-fixation bodies showed some binding in 2½ m.h.d. of complement only.

On the morning following the first dose of oral vaccine he had symptoms of a nasal cold coming on, with sneezing and a feeling of stuffiness in the nose. This, however, passed off during the day, and no cold developed. No symptoms were detected after the second dose. On the day following the third dose he noted general malaise, and slight toxic symptoms, with slight abdominal discomfort. After the fourth, fifth, and sixth doses he felt very general toxic symptoms and malaise, particularly after the last dose, when the symptoms persisted for three to four days.

Eleven days later a further series of six doses were commenced. After the first dose of this second series slight general toxic symptoms were again observed. Three days after the first dose a second dose of 20 c.cm. was taken by mouth. This was followed next day by general toxic symptoms, which lasted two days. It was then decided to wait a week before taking the third dose, as the symptoms suggested that the dose was either too large or being taken at too frequent intervals. At the same time, a week later, before taking the third dose the blood was again examined for the presence of agglutinins against Pfeiffer's bacillus. On this occasion the agglutination titre showed traces in 1 in 320 dilution of serum. For the third dose the amount of vaccine was reduced to 10 c.cm., and no symptoms were noted. The fifth and sixth doses consisted of 20 c.cm. at weekly intervals. No symptoms were felt after these intervals between the vaccine. A week later after the last dose there was definite agglutination up to a dilution of 1 in 640 and partial agglutination in a dilution of 1 in 1,280.

The Negative Phase

One of us (D. T.) took six doses of 20 c.cm. at intervals of two days. At the end of this course he felt ill, as if an attack of influenza was developing. These symptoms lasted for about twelve hours and then passed off quickly. The agglutination titre at the beginning of this course of oral vaccine was scarcely 1 in 10. At the end of the course the agglutination titre was 1 in 80. It was ascertained, however, that these broth cultures are very toxic even by mouth, and that one dose of 20 c.cm. should not be taken more often than about once in seven days. Otherwise negative phase follows on negative phase, and the desired increase in the agglutination titre is not produced.

Animal Experiments

It was found that 0.5 c.cm. of a living symbiotic blood broth culture of Pfeiffer's bacillus and *A. bronchitica*, injected intraperitoneally, killed white mice within twenty-four hours. Pfeiffer's bacillus was grown from the heart blood of the mice after death. Further, 0.5 c.cm. of filtrates, obtained by passing through a Berkefeld filter a four-day blood agar symbiotic broth culture of Pfeiffer's bacillus and *A. bronchitica*, when injected into white mice rendered them very ill for several hours, but did not kill them.

The two sera (E. T. T. and R. T.) which had shown a high agglutination titre against Pfeiffer's bacillus after oral administration were tested for their protective and neutralizing powers.

0.5 c.cm. of serum (E. T. T.) and 0.5 c.cm. of serum (R.T.) respectively were mixed with 0.5 c.cm. of a living forty-eight-hour symbiotic broth culture of Pfeiffer's bacillus, and the two mixtures each allowed to stand one hour in the incubator. At the end of this period two mice were injected intraperitoneally with each mixture. Both these mice showed no symptoms, and remained alive and well after forty-eight hours.

Two control mice, on the other hand, died. One injected intraperitoneally with 0.5 c.cm. serum, from a person who had not taken any oral vaccine, mixed with 0.5 c.cm. of the same forty-eight-hour symbiotic broth culture as above and incubated one hour, died during the night; the second mouse injected with 0.5 c.cm. of the forty-eight-hour symbiotic broth culture alone died overnight.

Prevention of Colds and Influenza with Oral Vaccines

The above results are significant, and indicate that specific agglutinins are formed to Pfeiffer's bacillus, and that antitoxins appear in the blood after oral administration of a killed carbolized symbiotic broth culture of Pfeiffer's bacillus. In order to avoid toxic symptoms whilst obtaining the maximum agglutination titre in the blood it would appear, however, that the doses of such a vaccine should be taken at about weekly intervals. We deduce that if agglutinins are formed to Pfeiffer's bacillus by the oral administration of symbiotic broth culture, the same would apply also to symbiotic broth cultural growths of pneumococci, streptococci, and *M. catarrhalis*. We have accordingly prepared a combined vaccine by separately growing Pfeiffer's bacillus, pneumococci (Types I–IV), streptococci, and *M. catarrhalis* in broth cultures in bacterial symbiosis with *A. bronchitica*.

One of us (E. T. T.) has taken four doses of this combined broth vaccine ranging from 10 to 20 c.cm. at weekly intervals. Five days after the last dose his serum

was tested for agglutinins against pneumococci and streptococci. No agglutinins were detected at the beginning of this course, but now, after four doses, his blood shows agglutinins for pneumococci in 1 in 40 dilution, and for streptococci in 1 in 80 dilution, thus indicating a definite agglutination response after the oral administration of such a combined vaccine. No toxic symptoms were observed with these doses at weekly intervals.

Secondary Organisms in Colds and Influenza

We record these results as they definitely indicate the practicability of the peroral method for prophylactic immunization against the various secondary pathogenic organisms associated with colds and influenza.

The importance of Pfeiffer's bacillus as a secondary organism in the respiratory complications of influenza and colds is now fairly conclusive. For although influenza and the common cold may in some instances be due primarily to a virus infection, all are agreed that it is chiefly the secondary organisms, particularly Pfeiffer's bacillus, pneumococci, and streptococci, etc., which determine the occurrence and severity of respiratory complications, and are the chief factor in causing the high mortality rate in influenza and in leading to serious chronic sequelae. The frequency of chronic nasal sinusitis due to pneumococci and Pfeiffer's bacillus after influenza and the common cold is now well recognized. It is also proved that many colds are caused primarily by pneumococci, Pfeiffer's bacillus, and other organisms.

Conclusions

The advantage of the oral route of administration over the subcutaneous method is obvious in that this method overcomes the practical difficulties associated with the latter. There is no doubt that there is a real need for such methods in public health work, when prophylactic immunization has to be applied to large masses of the population. Furthermore, it is much more convenient in every way to swallow a vaccine than to have it injected. A bottle of oral vaccine can be kept on the dressing-table in the bedroom of any individual, and the weekly dose can be swallowed in the evening, on an empty stomach, before retiring, the amount of time involved being only a few seconds. This weekly oral dose can be kept up all the winter without any trouble whatsoever, whereas the necessity of getting a medical man to inject vaccines weekly deters many people from trying such immunization.

The joint authors of this paper have been carrying out this procedure with regard to themselves since September, and we have the satisfaction of noting that we are keeping up our agglutinins to Pfeiffer's bacillus, pneumococci, and streptococci. None of us have had colds this winter so far, in spite of considerable exposure to infection.

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Clinical Memoranda

Haemolytic Streptococcus Gangrene

In 1924 Meleney[1] drew attention to haemolytic streptococcus gangrene as a clinical entity in a description of twenty cases occurring in China. He reported a further series of eleven cases in New York in 1930.[2] The condition is described as gangrene which develops with alarming rapidity and affects the skin and superficial tissues only, after small injury or apparently spontaneously. Haemolytic streptococci are the only organisms invariably found. Spontaneous haemolytic streptococcus gangrene of the scrotum has also been described.[3]

The condition is apparently rarely seen in this country. The case described below is typical, except for the destruction of deep tissues in the index finger.

Case Report

A farm labourer, aged 24, recommended by Dr. J. D. Macrae, Bonarbridge, was admitted to the Lawson Memorial Hospital, Golspie, on September 8th, 1935. The patient stated that on September 6th he worked all day in the harvest field and felt quite well. Apart from the usual abrasions and scratches received at his work he was unaware of injury to his hands. At 7 p.m. he suddenly felt sick and vomited. Shortly after going to bed he awoke with intense pain in his left hand; the hand and arm became rapidly swollen. At 5 a.m. on September 7th the pain became intolerable, and he went to see his doctor. Incisions were made in the dorsum of the hand then and again later in the day. Fomentations were applied, but in spite of energetic treatment the pain was not relieved and the swelling increased at an alarming rate. That night the patient suffered from much abdominal pain and sickness; on the following morning he was sent to hospital.

On admission he was gravely ill; the tongue was dry and furred, and herpes labialis was evident. The temperature was 103.6°, the pulse rate 104. The terminal phalanx of the left index finger was dark grey in colour and insensitive. Sero-pus oozed from the nail-bed and from incisions on the dorsum of the hand. The whole limb was enormously swollen, heavy, and useless. The skin was dusky purple, and bullae containing sero-pus were seen on the fingers, hand, and forearm. The appearance of the skin of the proximal arm gave no indication of the limit of the infection. On palpation the skin was hot and acutely tender; boggy areas were felt in the general brawny hardness of the upper arm and forearm. No definite lymphangitis or lymphadenitis was present.

Dr. R. G. Bannerman, from the pathological department, Royal Northern Infirmary, Inverness, reported that haemolytic streptococci were found in pure culture.

Treatment.—Routine treatment with salines, glucose, and collosol calcium was instituted. Anti-streptococcal serum (polyvalent) was given, 10 c.cm. intravenously on September 10th and 11th, and 10 c.cm. intramuscularly on September 11th and 12th.

The existing incisions were freely opened up, the successive bullae punctured, and all dead tissue removed. Antiphlogistine was applied, followed by antiseptic baths; later the raw areas were treated with metaphen 1 in 500 and dry dressings.

Progress.—On September 9th the skin and nail, complete like the finger of a glove, came away from the terminal phalanx of the left index finger, leaving the deeper tissues frankly gangrenous. The phalanx demarcated rapidly, and separated on the seventh day. Tissue destruction in the hand and arm was limited to the skin, which became lifted up by a sero-purulent exudate. This was demonstrated when pressure on the upper arm caused sero-pus to flow out of the incisions on the dorsum of the hand. On the seventh to tenth days sloughs separated, the temperature fell, and the general condition improved. Subsequently the patient made a good recovery, and in six weeks' time the wounds were practically healed.

Comment

The infection presumably originated from a small injury around the nail of this finger. Early incision is advocated as the best form of treatment, and doubtless the primary