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JENNER'S COWPOX INOCULATION*

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The introduction of vaccination as a prophylactic measure against smallpox by Jenner in 1798 was for many years the only successful application of active immunization in the prevention of infectious disease. The development of Jenner's method and its application to other infections by Pasteur 80 years later marked the beginnings of the science of immunology as we know it to-day. Great advances have been made in the last 20 or 30 years in the field of virus infections; but Jenner's method of immunization against smallpox still stands as the most valuable specific prophylactic measure against diseases caused by these agents.

The practical value of vaccination at the present time is perhaps not so immediately apparent as in Jenner's day, and to put the discovery in its proper setting it is necessary to consider briefly the morbid influence of smallpox at that time. The disease had been endemic in England for several hundred years, and early in the eighteenth century was said to be the cause of 70 to 80 out of every 1,000 deaths. During the course of the century, in spite of, some people think because of, variolation, to which I will refer presently, the ravages of the disease in no way abated. Haygarth in 1793 stated that in previous years the ratio of deaths from smallpox to births was as 1 to $6\frac{1}{2}$ in London, 1 to $6\frac{1}{2}$ in Manchester, and 1 to $5\frac{1}{2}$ in Liverpool. Most of the population were destined to suffer from the disease, and Haygarth records that after the outbreak in Chester in 1774 only one-fourteenth of the population had not had smallpox. The mortality from smallpox was then around 15 to 20% of cases, and most of the deaths occurred in children under 10 years. In Chester, from 1772 to 1777 inclusive, of 1,105 deaths in children under 10, 369—that is, one in three—were due to smallpox (Haygarth, 1793).

Inoculating the Smallpox

Variolation, or the practice of communicating smallpox artificially, was of ancient origin, and had apparently been used in Pembrokeshire before it became generally known to the public in this country through the activities of Lady Mary Wortley Montagu in 1721. It was based on the experience that, when the infection was transmitted by applying smallpox matter through scratches or incisions in the skin, the disease was likely to be much less severe than when contracted in the ordinary way. Variolation was used by lay people in Turkey

and Greece as well as in Wales and the Highlands of Scotland, but the medical profession were not practitioners of this measure. Lady Montagu had had her son inoculated with smallpox in 1717 by Mr. Maitland, surgeon to the embassy in Constantinople, where her husband was British Ambassador. In 1721, after the family had returned to London, she had her 4-year-old daughter variolated, again by Maitland. This event created some stir in medical and society circles in London; but, even after further trials on convicted felons and orphanage children and the variolation of two children of the royal family without untoward effect in 1722, the practice did not become popular.

It early became apparent that the method was not without risk. In October, 1721, Maitland inoculated Mary Batt, aged 2 years, daughter of a Quaker living near Hertford. The child had a mild attack of the disease, having only 20 pustules, and soon recovered. But six of the domestic servants contracted smallpox from the child and one of them died. Nor was the disease in the inoculated person always mild. The Earl of Sunderland's son, inoculated by Maitland in April, 1722, died of the infection. The introduction of variolation into Ireland in 1723 was particularly unfortunate, for of the first 25 inoculated in Dublin three died, two of these of haemorrhagic smallpox. In 1726 Maitland inoculated six children in his native Aberdeenshire, and one of these died; in this part of the country the practice was not again taken up for 20 years.

During the first eight years after its introduction only 897 were inoculated for smallpox in England, and of these 17 died. During the next 10 years inoculation was apparently little practised, but was again restored in England, apparently because of reports of its success in America. In 1746 public subscriptions were raised for the purchase of houses in London to be used as an inoculation hospital. This was not popular in the neighbourhood because of the fear of spread of the disease, and patients leaving after their stay of several weeks were abused and insulted in the streets, so that it became usual for them to leave in the hours of darkness. From 1751 variolation made uninterrupted progress, helped by a powerful sermon by the Bishop of Winchester in 1752 and by the approval of the College of Physicians, who considered the practice highly salutary to the human race. At this time the method of inoculation and care of the patients was such that the death rate from inoculated smallpox was less than 1 in 200.

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Improved Methods of Inoculation

The practice increased in popularity by the improvement in methods introduced by the Suttons, particularly by Daniel Sutton, who left his father to begin practice on his own in Essex and in Kent in 1763. Moore (1815) wrote of him: "Daniel Sutton with secret nostrums propagated inoculation more in half a dozen years than both faculties of medicine and surgery with the aid of the Church and example of the Court had been able to do in half a century." Dimsdale, himself probably the most successful medical practitioner of variolation, acknowledged his indebtedness to Daniel Sutton, whose methods he followed. Dimsdale (1781) attributed the success of Sutton to the method of inoculation by light scarification or puncture, the use of lymph from the primary vesicle of a previous patient or from an early vesicle in a casual case, the absence of dressing at the site of inoculation, the ambulant treatment followed, and the use of cold water to alleviate thirst at the febrile period. But while Sutton's innovations were to the benefit of his patients, the freedom of movement allowed them during the eruptive fever and afterwards tended to spread infection throughout the community.

As variolation was practised mostly among those of means, it was the poor who suffered from the increased prevalence of the disease. To minimize the risk of spread from inoculated persons Dimsdale and Haygarth recommended periodic inoculation of all those in a community who had not previously suffered from smallpox; those who were inoculated were enjoined, until they were recovered, to avoid contact with people who had not had the disease. Some of those variolated had no general eruption, but it was shown that the lesion at the site of inoculation might be the source of smallpox in immediate contacts; and the mildness of the disease in the inoculated did not necessarily ensure a similar benign course in those who acquired infection from them.

In spite of his success as an inoculator and the rarity of unfavourable results, Dimsdale later condemned the practice: "Though the loss under inoculation is very inconsiderable . . . yet by spreading the disease, a great proportion take it in the natural way; more lives are now lost in London than before inoculation commenced, and the community at large sustains a greater loss; the practice, therefore, is more detrimental than beneficial to society" (quoted from Monro, 1818). Even with the improved methods the fatality rate from inoculation towards the end of the eighteenth century was estimated at 1 in 250 to 1 in 500. Adams in 1807 wrote: "No patient is inoculated for smallpox without anxiety to the practitioner, the patient, and his friends"; and Woodville (1796) says of the early years of variolation: "That inoculation did not constantly succeed in producing the distinct or favourable kind of smallpox was at that time, and still continues to be, a melancholy truth."

Jenner's "Inquiry"

It is little wonder, therefore, that Jenner's method should have been so eagerly accepted as an alternative to variolation, although some of his medical brethren were unwilling to give up the older practice. For, as Jenner claimed, the cowpox inoculation was not infectious and did not carry with it the risk to the patient which variolation incurred. But let us consider for a moment the evidence on which Jenner's claim for cowpox inoculation or vaccination as a protection against

smallpox was based. The first cases listed in Jenner's *Inquiry* comprised 20 persons who had been infected by contact with diseased cows from less than a year up to 50 years before they were unsuccessfully inoculated with smallpox matter. In 11 of these variolation was attempted in the years 1791 to 1797, and one had been unsuccessfully inoculated in 1778. Three persons had become infected from horses. One, inoculated with smallpox matter six years later, failed to develop the disease, one developed a mild smallpox after variolation, and the third had a mild smallpox infection following exposure to casual infection. In addition to these there was one boy who was inoculated with cowpox vesicle fluid from the hand of Case 16; six weeks, and again several months, after he had recovered from the ensuing illness he was inoculated with smallpox vesicle fluid without effect.

In 1798 another boy was inoculated with matter from a cow, and from the resulting vesicular lesion on his arm the infection was passed in series through four more children. At the third passage several children and adults were vaccinated, and at the fourth three children; the fifth transfer was made to a boy 7 years old. Of this series three, including the last boy, were later inoculated with smallpox virus without effect. In his subsequent discussion Jenner points out the great advantage that inoculation of the cowpox would have over variolation, as it involved no risk of spreading a disease that filled the country with terror. None the less, Jenner realized that his evidence did not prove the case for cowpox inoculation, for he finished the *Inquiry* with the following sentence: "In the meantime I shall myself continue to prosecute this inquiry, encouraged by the hope of its becoming essentially beneficial to mankind."

Support for Jenner

Evidence in support of Jenner's observations was soon forthcoming. Within a few months of the publication of the *Inquiry*, George Pearson, a physician to St. George's Hospital, published reports by others who likewise had failed to variolate persons who had recovered from casual cowpox. When a fresh supply of cowpox lymph became available early in 1799, many people were inoculated in London by Pearson and Woodville, and, as lymph was widely distributed in England and on the Continent from this source, vaccination rapidly spread in spite of a certain amount of opposition. As the practice of variolation also continued for some years in the nineteenth century there was ample opportunity for testing the vaccinated by subsequent inoculation of smallpox virus. This was in fact done, and in the subsequent publications of Jenner (1801), Pearson (1802), Willan (1806), and others there are reported several hundred instances of people who had been vaccinated and in whom subsequent variolation failed to produce disease. Forty years later Robert Ceely (1842) gives details of 21 persons who had been successfully inoculated with a fresh cowpox strain that he had introduced and who were tested 5-31 months later with smallpox matter. None of these developed smallpox, though in some there was produced what we would now call an accelerated reaction.

In two points in the *Inquiry* Jenner probably erred in his conclusions. He expressed the belief that matter from an affection of the heels of horses known as "the grease," transmitted by the hands of men who also milked cows, was the source of cowpox; and that only

after it had passed to the cow did it "invariably and completely possess those specific properties which induce in the human constitution symptoms similar to those of the variolous fever, and effect in it that peculiar change which for ever renders it unsusceptible of the variolous contagion."

Jenner admitted that he had not been able to prove by actual experiment that the source of infection of the cow was a peculiar morbid matter arising in the horse; this supposed origin received no support from the experiments of subsequent observers, who failed in many attempts to induce cowpox in cows by inoculation with material from grease in horses. (As Crookshank (1889) has related at length, however, it was later shown by Loy, in England, Sacco, in Italy, and various observers in France that from horsepox, a febrile disease with a generalized vesicular eruption, humans and cattle could be inoculated with results similar to those following cowpox infection. From the infection of horses, equine strains of virus were brought into use for inoculation against smallpox by Jenner and workers on the Continent.) Nor was it long before it was shown that persons successfully inoculated with cowpox virus might later suffer from smallpox, though usually in a mild way. Details of such cases were published by Willan (1806), Adams (1807), and later by Monro (1818) and Cribb (1825). Cribb notes that smallpox in the vaccinated had been more frequent of late years—an observation not surprising in the light of present knowledge concerning the waning of immunity with the passage of time.

Establishment of Vaccination

Vaccination, however, quickly became much more widely practised both in this country and abroad than variolation ever had been. Cribb records in 1825 that the percentage of the population who had been vaccinated varied in different parishes between 34 and 69—a rate not achieved in diphtheria immunization until many years after the introduction of the method in this country. Vaccination was, however, carried on from arm to arm, and it appeared that as a result of repeated passage in this way the virus became uncertain in its effects. Vesiculation did not always result from inoculation. New sources of lymph were therefore sought and fresh strains from affected cows, or from milkers directly infected from cows, were introduced by Estlin (1837-8), Ceely (1840), and others. Such new strains produced much more vigorous local reactions, which took longer to heal and were frequently accompanied by axillary adenitis and fever; although Estlin (1839) noted that after 48 removes from the cow his strain had lost much of the activity it possessed when only 15 removes from the cow. Ceely tried retrovaccination of the cow in an attempt to rejuvenate stock strains of "humanized" lymph; but in this country it was not until near the end of the nineteenth century that virus propagated in the skin of calves received official approval for the preparation of vaccine lymph. Ballard (1868) notes that in Italy and France lymph had been kept going in cattle from 1863 and 1866 respectively. He also states that it was impossible to trace the origin of lymphs then in current use in England.

The viruses now used for the preparation of vaccine lymph in various establishments throughout the world, although possibly derived from cowpox, horsepox, or variola, are very much alike and are all referred to as vaccinia. These strains have been subjected to more detailed laboratory investigation than probably any other

virus. Vaccinia has a wide host-range and can be propagated in series, not only on the skin of calves and sheep in the preparation of lymph but in the common laboratory animals. The lesions are histologically similar to those caused by variola virus in man; but in man vaccinia is less virulent, rarely producing a generalized skin eruption. Although strains of vaccinia may have been derived from the natural pox disease of cows or horses, repeated propagation in vaccine lymph institutes has so modified them that they exhibit some characteristics not possessed by recently isolated strains of cowpox virus. This is referred to below.

Variola as a Source of Vaccine

In the belief that cowpox was essentially an infection of the cow by variola virus many attempts were made last century to infect cows with smallpox material. Most of these attempts were unsuccessful. Sometimes papular lesions appeared on the skin at the site of inoculation, but these could not be carried on in series, and when material from these papules was used to inoculate children smallpox, not vaccinia, resulted. The work on this subject was reviewed by Copeman in 1899 and more recently by Horgan (1938). A few workers claimed success; among them Ceely, who, after many failures, recorded in 1840 details of two successful experiments made with matter from seventh- or eighth-day smallpox pustules. From the vesicles which appeared on the inoculated cows children were vaccinated, and the lymphs from these were widely used with apparently good results. There must, however, remain some doubt about the nature of the virus which Ceely recovered from the cows. For in his first animal standard vaccine was injected in the neighbouring skin the day before a vesicle appeared at one of the sites of inoculation of variola fluid. His second successful animal was inoculated with smallpox vesicle fluid at a time when vaccine vesicles had developed at the vaccination sites in the first cow.

Badcock (1845), who inoculated 90 cows with smallpox material during a period of four years, used the lymph from occasional successful cases for the vaccination of children, and his lymphs were widely distributed. Details of Badcock's experimental procedure are not available. In later apparently successful experiments on the development of vaccinia from variola several transfers in the skin of the cow were necessary, as in the experiment of Copeman. Most French workers failed to obtain vaccinia from cows or rabbits inoculated with smallpox material. The successful results obtained occasionally by others have practically all been achieved in vaccine institutes, where the possibility of contamination with vaccinia can rarely be excluded. The observations of Kelsch and his colleagues (1909, 1910) showed the contagious nature of vaccinia for the cow. They found that, in a vaccine lymph institute, cows which had been inoculated in the scarified skin only with glycerin developed some days later a few vesicles which proved to be vaccinal. More recently the liability of rabbits to be infected with minimal vaccinal lesions when kept near experimentally infected animals has been recognized.

The monkey is the only experimental animal which can be readily infected with both variola and vaccinia viruses, and in the monkey variola apparently remains variola. But when variolous matter from the monkey is passed to the rabbit a vaccinal mutant is said to appear in this animal after several transfers. The

emergence of vaccinia is apparently facilitated by intra-testicular infection followed by inoculation of the testicular material on the scarified skin of fresh animals. Vaccinial strains were claimed to have been derived in this way by Amies in 1932 (personal communication) and by Horgan (1938), who took precautions to avoid the introduction of vaccinia from extraneous sources. The vaccinal strain obtained by Amies was later used for the preparation of vaccine lymph by Horgan (Horgan and Haseeb, 1945).

Variola strains do not apparently give rise to vaccinal mutants during prolonged cultivation on the chorio-allantois of chick embryos. Virus propagated in this tissue may multiply to some extent during repeated transfers in the testes of rabbits, but infectivity for the rabbit skin is not acquired (Nelson, 1943). Our own experience with a strain of variola in the form of crust extract or infected chorio-allantois and with egg-cultured alastrim virus has so far been similar to Nelson's. Both strains of virus multiplied in the testes of rabbits through several transfers without obvious clinical evidence of inflammatory reaction; but lesions on the skin reproducible in series could not be obtained by dermal inoculation of testicular material. Nor did the lesions on the chorio-allantois produced by virus from the testes of successive rabbits show any change towards the vaccinal type.

The role of monkey passage in the reported emergence of a vaccinal variant is not clear. That infection of the skin of the monkey merely increases the possibility of a vaccinal mutant emerging through increase of dose of virus to be inoculated in the rabbit seems unlikely; for direct inoculation of fresh human vesicle fluid rich in variola virus or of heavily infected chorio-allantoic suspension does not facilitate the appearance of vaccinia in rabbits. It may be that for the appearance of a typical vaccinal mutant more than one mutational step is necessary, and the first of these may take place in the skin of the monkey. Growth in the testis of the rabbit may provide suitable conditions for the emergence of further mutation, and the final step may occur as a result of the selective environment in the rabbit skin. The numerous failures to produce vaccinia by direct inoculation of smallpox virus from man to the skin of the rabbit or of the cow suggest that these tissues are so unfavourable to the continued growth of the human virus that there is no opportunity for the mutational steps necessary for the appearance of vaccinia.

The strain of vaccinia virus used for the routine preparation of lymph in this country is believed to have been derived from a case of smallpox in Cologne during the last century (McClean, personal communication), and one of the strains currently used in Uganda is said to be of variolous origin.

It seems, then, that vaccinia now used may be far removed from the cowpox of Jenner. What are the characters of cowpox virus recently derived from the natural infection in cattle, and how do they compare with those of vaccinia and variola viruses? I propose to consider briefly recent work bearing on this question.

Cowpox at the Present Time

Donaldson and Waldron (1951) state that only eight outbreaks of cowpox had been reported in this country during the last 50 years, although they believe that the disease is more prevalent than this suggests. This is certainly our own experience. From 1944 to 1950 we

have examined material from 10 different outbreaks of cowpox in different parts of England and Wales, and in each instance investigation of these incidents was occasioned by the affection of milkers. From this material eight strains of cowpox virus have been isolated, mostly from the human lesions. Outbreaks of cowpox therefore seem to be as common now as in Jenner's day, though smallpox is no longer an endemic disease. Nor is there any evidence that the disease in cattle originates from contact with recently vaccinated individuals.

Although the first description of the disease is contained in Jenner's *Inquiry*, it seems likely that it had existed for many years previously. Cowpox is milder than the pock diseases of other animals; the lesions are confined to the teats and udders, spread within a herd being effected mainly by the manipulations during milking. The nature and history of the disease and the characters of the virus indicate that cowpox is an infection peculiar to the cow. It seems that the infection, apart from the process of milking, might often be latent. The mild nature of the lesions in the cow and the possibility that the disease is kept going by the persistence of trivial infection in immune animals, as in herpes simplex infection in man, might be regarded as evidence that cowpox in cattle has a very long history.

The disease now to be seen in cows and that contracted by milkers conforms to its first description by Jenner and to the later detailed account of Ceely (1840). The lesions in milkers usually occur on the hands, often between the thumb and first finger, but may be seen on the forearm or face. In unvaccinated persons the disease generally runs a more severe course than that which follows primary vaccination in adults (Davies, Jones, and Downie, 1938), and the local lesion is often associated with lymphangitis, lymphadenitis, and some degree of fever and general upset. Healing of the lesions may take several weeks, but fatal infections have not been recorded.

The appearance of the vesicles on human skin is similar to that of vaccination vesicles, although there is more congestion and the contents may be blood-stained. This tendency to haemorrhage was noted by Jenner and by Ceely in the vesicles of cows and of milkers. Histologically, the cowpox vesicle has the same general appearance as the vaccination and smallpox vesicle. In the epithelial cells at the base of the lesion, however, in suitably stained sections there are strongly acidophilic compact intracytoplasmic inclusions which differ from the inclusions of the vaccinia or variola lesion. Laboratory animals and developing chick embryos can readily be infected with vesicle fluid from human lesions. The animal pathogenicity and experimental host range of cowpox virus is similar to that of current strains of vaccinia and is less restricted than that of variola virus. The lesions in experimentally infected animals always have a haemorrhagic character, which is not a feature of lesions caused by dermal strains of vaccinia. In skin epithelium and in mesodermal cells, including vascular endothelium of the underlying cutis, the typical cytoplasmic inclusions are constantly found (Downie, 1939).

Immunological Relationship between Cowpox, Vaccinia, and Variola Viruses

It has been shown by various workers that, in animals, infection with cowpox or with vaccinia virus produces immunity of similar degree against both viruses. Sera

from animals immunized against either virus neutralize both viruses in the rabbit skin, but minor serological differences have been elicited by cross-absorption of immune sera with the two viruses. Cowpox virus removes from an antivaccinia serum agglutinating, complement-fixing, and neutralizing antibody for cowpox more readily than it removes corresponding antibody for vaccinia virus; the converse holds for the absorption of cowpox antiserum with vaccinia virus.

Variola virus cannot be used for comparative immunological studies in the usual experimental animals because of its very limited pathogenicity; such studies made in monkeys have shown immunological similarity between strains of vaccinia, variola, and alastrim (see Gordon, 1925; Horgan and Haseeb, 1939). Variola and alastrim viruses can, however, be readily propagated on the chorio-allantois of developing chick embryos, where they cause typical focal lesions which are different from those produced by vaccinia and cowpox. In Liverpool my colleagues and I have made serological studies of these viruses, using human convalescent sera and virus preparations from smallpox crusts or from infected chick chorio-allantois. Experiments have also been carried out with immune sera prepared in fowls by injections of virus propagated in chick membranes. By complement fixation and inhibition of complement-fixation techniques the viruses of alastrim and variola could not be differentiated. Vaccinia virus was also closely related. There was considerable cross-reactivity between cowpox virus and the variola-vaccinia group, but this virus showed more divergence from variola than did vaccinia (Downie and Macdonald, 1950).

In neutralization tests on the chorio-allantois, using human convalescent and animal immune sera, immunological differences between these viruses could not be readily demonstrated by the usual technique. The use of absorbed sera elicited minor antigenic differences of a nature similar to those shown by the *in vitro* techniques (Downie and McCarthy, 1950). Recently we have tested the cross-neutralizing power of convalescent sera from three unvaccinated smallpox patients and from three unvaccinated persons who had recovered from cowpox infection contracted from cattle. The cowpox virus used had been isolated from a cow and passed three times on eggs, and the variola strain from smallpox crusts had been passed five times on eggs. The results (see Table) showed that the smallpox convalescent sera

Neutralization of Cowpox and Variola Virus by Convalescent Sera from Cowpox and Smallpox Patients

Convalescent Sera	% Reduction of Virus Lesions on Chorio-allantois	
	Cowpox Virus	Variola Virus
Cowpox 1	73	74
" 2	93	84
" 3	89	77
Smallpox 1	88	95
" 2*	80	44
" 3	89	93

* Serum taken on eighth day of illness.

neutralized both viruses, and the sera from the cowpox patients neutralized variola virus practically to the same degree as they neutralized cowpox virus. The results with these sera from unvaccinated persons confirm the immunological similarity between cowpox and variola virus; a finding which supports Jenner's contention that those who have suffered from cowpox are thereby rendered immune to smallpox.

In summarizing our knowledge of these three viruses we can say that there is a close immunological relationship between the viruses of variola, the natural pock disease of man, and cowpox, the natural pock disease of bovines, although the diseases are clinically and epidemiologically so different. Variola is an acute generalized infection, highly contagious, whereas cowpox is mild with only a local eruption and is not contagious. The skin lesions in the two diseases are histologically similar, although those of cowpox are more constantly haemorrhagic and the virus inclusions are different in appearance. The virus of variola is much more limited in its experimental host range, being infective for the monkey and the chick chorio-allantois but not readily causing infections reproducible in series in other animals.

Strains of the artificially propagated vaccinia virus are immunologically related to both variola and cowpox virus. It is practically identical in this respect with variola and shows minor serological differences from cowpox. The lesions produced by vaccinia in the skin of man and animals are histologically identical with those produced by variola in human skin, and the inclusion material has the same appearance. On the other hand, vaccinia strains resemble cowpox virus in that they have the same wide experimental host range and in man do not usually produce generalized skin eruptions and are not contagious. The differences between cowpox and vaccinia viruses do not seem to be fundamental, and it seems possible that by the repeated artificial propagation of cowpox virus in animals or on the skin of man a virus with the characters of vaccinia could emerge.

Conclusion

In a recent publication Professor Kaiser (1949) laments: "That the English are now discarding [*ablehnen*] the life work of one of their most famous sons is a tragedy that we can only note without comment." But we have not discarded Jenner's work. Although compulsory vaccination has recently been abolished in this country because of the greatly lessened risk of smallpox, a risk lessened in some measure by Jenner's labours, we still recognize the great value of vaccination in protecting those exposed to infection; and Jenner's vaccination is an essential part of the procedure adopted to prevent the spread of smallpox in this country when infection is introduced from abroad. Greenwood (1935), after a critical discussion of the statistical evidence on the value of vaccination in lessening the ravages of smallpox, concludes that Jenner was, directly or indirectly, the means of saving many hundreds of thousands of lives; a conclusion, he submits, quite enough to entitle Englishmen to take pride in the recollection that Jenner was their countryman.

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IDIOPATHIC HYPOCHROMIC ANAEMIA IN YOUNG ADULT MALES

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Idiopathic hypochromic anaemia is described by Whitby and Britton (1946) as a chronic anaemia chiefly found in middle-aged women and characterized by a low mean corpuscular haemoglobin concentration and mean cell volume; achlorhydia and glossitis are usual, while koilonychia is common. Attention was first drawn to the condition by Faber (1913) and since that time ample descriptions of the disease in women have appeared in the literature.

According to Whitby and Britton the disease is uncommon in males, while Wintrobe (1946) states that 4% of cases are found in men. Faber's original account of 22 cases contained three males. Witts (1930a) analysed a series of 50 cases, one of which was a man; while Davies (1931a) later reviewed the subject of achlorhydia and anaemia and found no males in a series of 15 cases of hypochromic anaemia. In a further series recorded by Davies (1931b) there were four males in a total of 55 cases. Parkes Weber and Weisswange (1933) described four cases of anaemia of unexplained origin occurring in men, only two of which were of the true hypochromic type. Bethell *et al.* (1934) found two males in a series of 33 cases; Britton (1936) recorded four cases of idio-

pathic hypochromic anaemia occurring in men in a series of 66. Reviewing the incidence of chronic nutritional anaemia, Davidson and Fullerton (1938) found no cases in a series of 167 adolescent and adult males, while the Medical Research Council (1945) showed that between 2 and 3% of adult males had a haemoglobin level below 80%, and 0.2% of adolescent males under the age of 20 years had a haemoglobin level below 70%. In that survey no cause was apparently sought for the anaemia.

The occurrence of idiopathic hypochromic anaemia in the young adult male is, however, very rarely described. Wintrobe states that of the cases occurring in men, 82% are found between the ages of 20 and 50 years. Thomson (1943) recorded nine cases occurring in adolescent males whose ages ranged from 17 to 19 years, and Beckert (1938) described two cases of apparent chlorosis in youths aged 16 and 17. The five cases of chlorosis recorded by Witts (1930b) were found in young men with ages varying from 18 to 28 years, while of the series of 26 cases of idiopathic hypochromic anaemia in males described by Witts and Burger (1934) eight were males below the age of 30.

The present series of 20 cases in young soldiers has been seen by us over the course of the past two years at the Cambridge Military Hospital, Aldershot. Although the ages of patients (all male) attending the hospital range from 18 to 60 years, cases of idiopathic hypochromic anaemia have been observed only in soldiers from 18 to 23 years of age. All but one of the cases were found in men with less than three months' service, and an interesting point for which we can offer no explanation is that of the 20 patients 11 came from the Royal Army Ordnance Corps. In none was there any relevant past history, and in one case only was there any familial history of anaemia. This man had an anaemic brother. On close questioning no abnormal food habits were found. Clinical examination and special investigations revealed no evidence of gross organic disease such as chronic infection, gastro-intestinal disorders, chronic nephritis, recurrent rheumatism, or neoplasm. A particular search for gastro-intestinal haemorrhage or bleeding haemorrhoids failed to disclose a cause for the anaemia.

A summary of the main clinical findings is shown in Tables I and II. Some representative case histories are given below.

Case 5

Aged 19. Service, one week. Civilian occupation, plasterer's labourer. History: was examined one year previously by civilian medical board and call-up deferred owing to anaemia; not investigated, but advised to take iron tablets, which he did not do; no symptoms before joining Army, but marked dyspnoea on exertion since recruitment; had "gastritis" five years previously; no relevant family history. Physical examination: mucous membranes very pale; sparse axillary and pubic hair, fine in quality; skin thick and dry, nails fluted; tongue, teeth, and pharynx healthy; spleen just palpable; no haemorrhoids.

Investigations.—Hb, 7.6 g.% (Sahli); R.B.C., 5,000,000; C.I., 0.52; P.C.V., 32%; M.C.V., 64 μ^3 ; M.C.H., 15.2 μg ; M.C.H.C., 23.7%; W.B.C., 6,400 (P. 54%, L. 42%, M. 2%, E. 2%); red-cell fragility within normal limits; chest radiograph normal; F.T.M., histamine-fast achlorhydia; stools, negative for O.B. (six specimens).

Treatment: ferrous sulphate, 6 gr. (0.4 g.) t.d.s.; dilute HCl, 15 min. (0.9 ml.) t.d.s., a.c. Result: Hb, 14.2 g%; R.B.C., 4,800,000; C.I., 1, after 11 weeks; no return of symptoms after two years.