THE ETIOLOGY OF RICKETS:

AN EXPERIMENTAL INVESTIGATION.

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(Abstract.)

SINCE 1907 investigations upon experimental rickets in dogs have been carried on in this laboratory, first by Leonard Findlay,¹ then by Renton and Madge Robertson,² and subsequently by Noël Paton, Findlay, and Watson.³

These last experiments showed that while all the pups of two litters kept in the laboratory upon an abundant supply of whole milk and oatmeal porridge developed rickets, two pups from each of the litters kept in the country on skimmed milk and oatmeal remained free of the disease.

The present series of observations* shows that pups kept in the laboratory develop rickets even on an abundant supply of milk fat (as much as 7.5 or even 11 grams per kilo) and oatmeal porridge, but that those on the same amount of separated milk (0.2 to 0.7 gram of milk fat) and porridge develop the disease more rapidly. The energy value of the separated milk diet was necessarily lower than that of the full milk diet (207 to 267 calories as against 270 to 437 calories), and hence it is possible, as is suggested by the observations on infants by Hess and Unger,⁴ that a low energy intake may predispose to the disease, although it is not a causal factor.

To test this the next experiment was arranged so that pups of three litters, which were available at the time, should have the diet increased proportionately to their increase in weight, and that the energy intake should be kept ample throughout the period of growth, but that, while one series of pups should have the energy supplied largely from whole milk—fresh and dried—with bread, another should have it from dried separated milk and bread, another from lard, which the Vitamin Committee⁵ of the Medical Research Council class as a fat free of their anti-rachitic vitamin, and the last series from dried separated milk and bread. Scrupulous care as to cleanliness was observed throughout this experiment.

The result was that all the pups, with one exception, reached fifteen to eighteen weeks free of rickets, although those upon the separated milk and bread diet had only 0.3 to 0.6 gram of milk fat per kilogram per day.

The basis of Mellanby's⁶ experimental work is that separated milk up to 250 to 350 c.cm. and white bread, even with linseed oil, yeast, and orange juice, will not prevent the onset of rickets in pups between six and twelve weeks of age, while whole milk will prevent it, and upon this is based the practical recommendation of the Vitamin Committee,⁵ p. 99, that full cream milk should be used by children for the prevention of the disease.

Butter is placed with cod-liver oil (p. 102) as the substance richest in "fat-soluble A or anti-rachitic factor," but both of the two pups in our series to which butter was administered in large quantities developed rickets, while its administration failed to cure or to prevent the advance of the disease in another.

Our experience indicates that by attention to strict cleanliness it is possible to rear pups free from rickets in a laboratory. It is easy to rear them in the open air, even on a diet poor in milk fat. The work of Morpurgo on white rats, and the study of an epidemic of rickets among foxhounds in Adelaide by Bull,⁷ taken along with our results, point to the probability that a bacterial infection of the same non-specific character as that which the investigations of McCarrison have shown to be the causal factor in goitre, plays an important part in the etiology of the disease.

A point of considerable interest demonstrated in our observations is the more rapid growth of the pups kept in the open air.

* A detailed account of the experiments is published in the April number of the *British Journal of Experimental Pathology*. The expenses of the investigation were defrayed by the Medical Research Council.

CONCLUSIONS.

1. In young dogs, under ordinary laboratory conditions, a liberal allowance of milk fat up to even 14 grams per kilo of body weight neither prevents the onset of rickets nor cures it when it has developed.

2. Pups kept largely in the open air may escape the development of rickets on an intake of less than 1 gram of milk fat per kilo body weight.

3. With scrupulous care as to cleanliness it is possible to rear pups free of rickets in the laboratory on an intake of only about 0.5 gram of milk fat per kilo of body weight, along with bread, provided that the diet affords an adequate supply of energy.

4. The energy value of the diet, however supplied, quite apart from the presence of any hypothetical anti-rachitic factor in milk fat, would seem to play a part in controlling the development of rickets, but that it is only a contributory part is shown by the development of rickets in pups with a high energy intake when they are confined in the laboratory without scrupulous care as to cleanliness.

5. Milk fat may be reduced to about 0.3 gram per kilo of body weight, if its place is taken by an equal amount of lard, without the onset of rickets.

6. The results of these observations do not support the conclusion of the Accessory Food Factors Committee of the Medical Research Council that rickets is a deficiency disease due to lack of an anti-rachitic factor associated with milk fat.

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A TUBERCULOSIS IMMUNIZING VACCINE.

BY

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OF all the serious infections of the human body tuberculosis is the most hopeful, both as regards its prevention and also its cure, provided that treatment can be commenced early enough and continued long enough to give the affected tissues time for repair.

In spite of an enormous amount of research, continued in all parts of the world, we have reluctantly to admit that we have not yet obtained a specific remedy which will effectively destroy tubercle bacilli in the body. We must therefore rely on producing a sufficient immunity in the tissues to resist the attack by virulent tubercle bacilli. This immunity can be obtained:

1. By increasing the natural resistance by means of increased nutrition and sound hygienic conditions.
2. By producing an artificial active immunity in the tissues to the tubercle bacillus itself.

Increased care in infant welfare, better wages to the industrial classes, good nourishing food, a pure milk supply, the prevention of overcrowding, and, above all, good housing conditions and the segregation, of open cases of pulmonary tuberculosis, will obviate to an increasing extent the possibility of direct infection; but all this will take many years to accomplish. In the meantime I feel strongly, from my experience of treating many thousands of cases of tuberculosis in hospital, that we have at our disposal a scientific means by which we can secure some immunity to the bacillus, and certainly of preventing the extension of the disease in the human body when once introduced. Fortunately for civilization, the tubercle bacillus is a parasite and not a saprophyte. It has no existence outside the living body, otherwise the whole community would be endangered.

In the *BRITISH MEDICAL JOURNAL* of 1903 I published a preliminary note, the gist of which was that human and bovine tuberculosis were separate and distinct infections, producing a different set of symptoms in the human body. The lesions caused by the human bacillus (direct infection)

are pulmonary tuberculosis, tuberculous laryngitis, secondary intestinal ulceration, and, in some cases, lupus. The lesions due to the bovine bacillus, and generally caused by infected milk in the early years of life, are tuberculous glands, mesenteric tuberculosis, surgical tuberculosis of bones and joints (frequently), tuberculous meningitis, and some cases of lupus.

I still hold to this classification and differentiation of the effects of the two forms of bacilli, and, in addition, I firmly believe that the one form confers an immunity in the body to the other. In fact, the two varieties of bacilli will not exist together in the body at the same time.

To some extent this is of great importance in treating the disease, as we are only able to produce immunity in animals by using human bacilli of ordinary virulence, or by attenuating the bovine bacillus to such an extent that it is non-pathogenic.

After treating over 2,000 cases of tuberculosis in hospital with Koch's tuberculin, prepared from virulent cultures, I came to the conclusion that, although a certain amount of success was obtained, the results were not on the whole satisfactory. The uncertain action of the tuberculin and the alarming reactions sometimes produced were very disconcerting, and there is no doubt that in some cases quiescent tubercle was stirred to acute activity.

For this reason I came to the conclusion that it was essential to use cultures of very low virulence, and to avoid, if possible, general febrile reactions. The only certain way of permanently attenuating virulent cultures of tubercle bacilli is by long-continued and systematic subculturing spread over a number of years. In 1906 Professor Koch gave me in Berlin a pure culture on glycerin agar of human bacilli from the sputum of an advanced case of pulmonary tuberculosis. Professor Calmette supplied me with a pure culture of bovine tuberculosis obtained from the mesenteric glands of a cow, and Professor Bang of Copenhagen gave me a pure culture of avian bacilli from the liver of a chicken.

These cultures have been subcultured on glycerin potato and then transferred to glycerin agar, every month for fourteen years in my laboratory, and the present growths represent the 184th generation. The growths are still profuse and true to type, but they are quite non-tuberculinogenic and completely non-pathogenic to animals. Every year since 1906 I have injected these bacilli into animals with a view to testing their pathogenicity. Until the year 1912, that is, the 94th generation of subcultures, I noticed no change in their virulence. After that time attenuation became marked, and in a series of animal inoculations of these bacilli in 1913 and 1914 they were observed to be avirulent.

The war interfered seriously with my experiments, but I took the cultures to France and continued the work there for four years, inoculating hares, rabbits, and guinea-pigs in 1916 and 1917. The cultures were in all cases non-pathogenic. In 1919 I inoculated more animals at the Lister Institute, and although large doses were given, no infection whatever was conveyed, and the animals remained alive and well for four months.

These experiments, which have occupied me for fourteen years, conclusively prove that virulent tubercle bacilli can be attenuated to such a degree as to be avirulent and non-pathogenic to highly susceptible animals, and in my opinion we have in our hands a remedy against tuberculosis which will be of the greatest value, not only in the cure of the disease, but what is of still greater importance, in its prevention, by protecting the human body against attack.

Natural attenuation, while removing the virulence and toxicity of the organism, enhances the value of the vaccine in the treatment of disease. In the case of small-pox the immunity derived from an inoculation of the virus from the pustules of vaccinia is considerably greater than that which results from an attack of variola, because the defensive elements in the body have not been weakened in overcoming the virulence of the toxin.

Treatment of disease by vaccines prepared from organisms attenuated naturally means that the production of antibodies will take place rapidly without any preliminary shock to the system such as invariably follows the injection of a vaccine prepared from a virulent strain of bacteria. Hitherto it has not been possible to test this in

tuberculosis, owing to the length of time necessary to produce a non-pathogenic strain of the tubercle bacillus.

The results of my work on animals conclusively prove that immunity against infection is produced by the injection of attenuated bacilli, and it is reasonable to suppose that the same thing will hold good in the human. Cattle can be rendered immune to virulent bovine bacilli by previous inoculation with virulent human bacilli; and I am convinced that there is a marked antagonism in the human body between human and bovine infections. It is an indisputable fact that these two organisms cannot flourish in the body at the same time. A child who develops primary abdominal tuberculosis with involvement of the mesenteric glands, or an infection of the neck glands, which are usually caused by the bovine bacillus conveyed in tuberculous milk, is immune to infection by the human bacillus for the remainder of life, and young adults attacked by the human bacillus, producing primary pulmonary tuberculosis, are immune to bovine infections for the rest of life.

The scientific means at our disposal at present for the accurate differentiation of human and bovine infections in the body are not sufficiently accurate to be decisive. There are atypical strains of bacilli which cannot be classed with certainty in either group, and the varying virulence of these bacilli and their effect on susceptible animals is still a matter of some uncertainty in a fair number of cases.

With a view to elucidating this doubtful point as to the real amount of tuberculosis in man caused by these two types of bacilli, and also as to the immunity produced by one infection towards the other—in other words, in order to obtain an answer to the question whether the disease caused by the human bacillus is antagonistic to that caused by the bovine bacillus and vice versa—I instituted clinical observation on a large scale in a Liverpool hospital containing 900 beds, of which I had sole charge for eighteen years. During that time I had the opportunity of treating over 10,400 persons suffering from tuberculosis in all its various forms.

Two hundred beds were devoted to tubercle. Half of these were cases of primary pulmonary tuberculosis; the other half of surgical tuberculosis—glands, bones, joints and lupus. During a period of thirteen years 4,800 cases of phthisis passed through the human wards and 1,820 cases of surgical tuberculosis passed through the bovine wards—a total of 6,620 patients.

The object of the observation was to see what other lesions, if any, were developed in the patients suffering from pulmonary tuberculosis, and how many of the surgical cases developed lesions in the lungs. I was assisted in this work by many excellent house-physicians and nurses, and the results were very striking and important.

In no case of primary pulmonary tuberculosis did we observe during the course of illness tuberculosis of bones, joints, glands, or skin, nor any instance of meningitis. Several cases developed brain symptoms in the last stages of the disease, but they were due to insanity, toxæmia, or exhaustion, and of the cases with meningeal symptoms, those examined *post mortem* were found to be cases of pneumococcal meningitis.

Amongst the surgical cases of tuberculosis 28 developed lung symptoms, and these were all examined by laboratory methods and animal inoculation; 25 died and were carefully investigated *post mortem*. In all cases the infection of the lung was either by direct extension from cervical glands to the apex of the lung, or from a primary focus in the abdomen extending upwards through the diaphragm to the bronchial glands and lungs.

This large clinical experiment convinced me that the human body is attacked by two quite distinct forms of tuberculosis—the one conveyed from person to person by direct infection and attacking chiefly the lungs, or so-called consumption, and the other conveyed by milk from tuberculous cows, and developed in the first few years of life.

These two diseases are caused by different types of tubercle bacilli which will not live in the body at the same time, and, what is of the highest importance, one disease produces immunity to the other.

I have emphasized this point of antagonism between the two infections to show my reason for always using a vaccine prepared from bovine cultures in the treatment of the human infections and vice versa.

The varying degree of virulence of the attacking organism is of supreme importance. The great majority of cases of tuberculosis are fortunately of low virulence, and, given suitable conditions, are favourable for treatment; but in some cases the virulence is so high as to destroy the person in a few weeks or months, and these are the cases popularly known as galloping consumption.

From my own observation I am inclined to think that in this country the virulence of the tubercle bacillus is less than it was thirty years ago. The number of deaths in England and Wales from tuberculosis in 1920 was 12,000 less than in 1919, a most gratifying record of progress in dealing with this terrible disease, which destroys 60,000 lives each year in England alone.

A large percentage of the population receive at some period of their lives a mild infection of tubercle which, in many cases, produces no definite symptoms. These persons recover, and are to some extent immunized against a further and more severe infection.

If we can induce some immunity by artificial means in children whose parents or relatives are tuberculous, and who by constant association with them are very liable to infection, we will have gone a long way towards stamping out tuberculosis. As Roemer says, "The most important problem in the prophylaxis of consumption is the saving of children in phthisical homes from severe tuberculous infection."

The vaccine which I have had prepared from these attenuated cultures is a bacillary emulsion of the bacilli, and contains all the products of the bacillus. It is non-toxic and avirulent, and produces no reaction even in large doses.

For purposes of immunization in susceptible children six injections are given at weekly intervals, and repeated in three months. The doses recommended are 0.001, 0.002, 0.003, 0.004, 0.005, and 0.006 mg. No symptoms whatever have been observed to follow these injections.

In the treatment of the active disease the doses used are much larger than have been possible hitherto; it is recommended that the treatment should consist of at least twelve injections given in increasing doses at intervals of seven days. The doses commence at 0.001 and increase to a maximum dose of 0.025 mg. The vaccine should be freshly prepared from the cultures, and should not be used after one month.

Our chief object in the treatment of active tuberculosis is to limit the spread of the disease in the organs. If we can locate a recent deposit in the apex of a lung, and prevent its extension throughout one or two lobes, the patient will have a good chance of recovery, and I maintain that we can only do this if we can provide his blood with some active immunity with which to resist the infection.

This vaccine, prepared as it is from avirulent cultures, can be used with complete safety in any stage of the disease, and even in advanced cases I have observed great relief from night sweats, toxic symptoms, and erratic temperatures. I have treated 118 cases of tuberculosis with various forms of the products of these attenuated bacilli, but I have decided that the bacillary emulsion is the best preparation.

The results in suitable cases are excellent, but it would require at least two years to gauge accurately the effect of the vaccine for purposes of immunization.

I have succeeded in completely immunizing highly susceptible animals against tuberculosis by the use of attenuated cultures which have required fourteen years' subculturing in the laboratory, and I firmly believe that if all children with a tuberculous history could be safely vaccinated in the manner I have described they would be placed in a better position to resist infection at home.

Prevention is better than cure; and if we are to eradicate consumption, as I firmly believe we will, it can only be by preventing infection of healthy people, and especially children, rather than by devoting all our energies to the cure of those already infected.

The amount of tuberculosis conveyed to infants and young children in milk derived from dairy cows suffering from tubercle is enormous. It is estimated that over one million dairy cows in this country alone are tuberculous, and there seems to be no improvement in this disgraceful state of affairs. The simple process of raising the temperature of the milk to 190° F. makes it perfectly safe,

and does not in the slightest degree impair its nutritive value. Sterilized and proprietary milks are quite safe, and free from tubercle, and should be used in preference to unboiled cow's milk.

THE SURGERY OF THE PERIPHERAL NERVE INJURIES OF WARFARE.*

BY

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ANALYSIS OF A PERSONAL SERIES OF OPERATIONS.

General Survey.

AN analysis of the total operations performed in my services in the period from March, 1915, to December, 1920, is given in Table I. The figures may be taken as representative of an average individual operative experience, and it is therefore safe to refer briefly to certain general information that the statistics themselves afford.

The frequency with which the ulnar nerve called for treatment, the infrequency of operations on the brachial plexus, and the complete absence of any operation on either the musculo-cutaneous or circumflex nerves in the upper limb, or the anterior crural nerve in the lower limb, are facts to be noted.

In the various types of operation the phases through which the operator passed are illustrated in the large number of operations of the bridge type, and those in which repair was abandoned.

Analysis of Results.

Of the operations in this series it has been possible to investigate the early and later results over periods extending from six months or more in 248 only.

It must be admitted at the outset that this study includes few if any *true* end-results. The most reliable records in our possession are those of the operations performed since 1917, when the advantages of a more efficient segregation of the patients, and the inauguration of the follow-up system were available. But though the conditions were such as in civil surgery might be considered ideal, the greater number of the patients could be kept in hospital for short periods only, and were then distributed in various parts of the country. This difficulty, which has been experienced by all surgeons, explains the comparative paucity of the operation statistics hitherto available.

TABLE I.—Total Operations.

	Suture.	Neurolysis.	Bridge.	Repair Abandoned.	Partial Suture.	Exploration: No Lesion.	Exploration: Nerve left in situ.	Injection.	Exploration: First Stage.	Total.
Brachial plexus ...	5	4	—	—	—	2	—	—	—	11
Musculo-spiral ...	51	15	5	14	—	1	—	—	—	87
Median ...	70	45	6	—	5	2	—	1	1	132
Ulnar ...	115	49	12	—	—	1	5	—	—	182
Posterior interosseous	1	—	1	—	—	—	—	—	—	2
Sciatic ...	51	9	3	—	2	1	—	—	4	70
External popliteal ...	14	2	—	6	—	—	—	—	—	22
Internal popliteal ...	—	2	—	—	—	—	—	—	—	2
Posterior tibial ...	—	1	1	—	—	—	—	—	—	2
Total ...	307	127	28	20	7	7	8	1	5	510

Operations for severe causalgia, 25—

Median 14

Sciatic 10

Internal popliteal 1

Operations in which end-to-end suture failed, 53.

Successful suture at second attempt, 1.

Failure of suture at second attempt, 3.

* Part of a Hunterian Lecture on The Results of Operations for the Repair of Nerve Injuries, delivered before the Royal College of Surgeons of England.