3. By means of laboratory methods it can be demonstrated that the incidence of syphilitic infection is much greater than had been suspected. The percentage has been raised by 12·1 in the case of the Manx patients and by 15·0 for the Scottish hospital.

4. Better conclusions can be arrived at when a greater number of mental hospitals are available for comparison, but a true index can only result if the observations are made by the same author.

I am indebted to Dr. Skene, Superintendent of the Manx Mental Hospital, and Dr. Ross, Superintendent of Argyll and Bute Mental Hospital, for giving me the opportunity of carrying out this investigation in their hospitals, and I am especially indebted to Prof. Mackie for facilities in connection with the laboratory work.

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Mendelism in Bacteriology.[1] By F. H. Stewart, M.A., D.Sc., M.D., D.P.M., Major I.M.S. (ret.), Assistant Medical Officer, Cheddleton Mental Hospital.

The studies which I wish to bring to your notice were begun with the object of finding some bacterial cause for manic-depressive insanity. This problem has, of course, engaged other laboratories. I would refer particularly to the work done in the Cardiff Laboratory, which has been described by Goodall in the Journal of this Association.

Our work in Cheddleton was given a particular direction by the first case examined, in which we found a very striking change in the intestinal flora—a change which developed and receded in exact parallelism with the maniacal exacerbations. During the attacks *Bacillus coli communis* disappeared from the fæces, and two microbes known as *Bacterium coli mutabile* and *Bacillus paracoli* appeared in

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its place. The same alteration was found in several other cases. But observations extending over the past four years have shown that the parallelism is not absolute. Some patients never exhibited the change at all, others exhibited it in one attack and not in another. It therefore became clear that we were not dealing with the cause of the disease, but with a concomitant or resultant phenomenon.

Nevertheless the facts were sufficiently striking to justify continued work along these lines, and we have therefore studied the life-history of the two abnormal forms, *Bacterium coli mutabile* and *Bacillus paracoli*, in some detail, hoping that increased knowledge would explain the mechanism of the change in the flora.

I do not propose in this paper to enter into details which are of interest only to professed bacteriologists, since a full account of the matter will, it is hoped, appear shortly in the *Journal of Hygiene*, but a few outstanding technical facts must be given to make clear the general conclusions at which we have arrived.

In the first place both *Bacterium coli mutabile* and *Bacillus paracoli* differ from *Bacillus coli communis* in that they lack the power of fermenting lactose. They belong to the group of non-lactose fermenting bacilli, which also includes the bacilli of dysentery, typhoid, paratyphoid, and food-poisoning, while *Bacillus coli communis*, on the other hand, belongs to the lactose fermenting group.

In the second place *Bacterium coli mutabile*, but not *Bacillus paracoli*, possesses to a remarkable degree the power of variation, and this power is exhibited by its formation of daughter races differing from the parent in their ability to ferment lactose. The daughter races have, in fact, become identical with *Bacillus coli communis*.

The credit of establishing these facts is due to the German bacteriologists Neisser and Massini, and their work has been extended by Arkwright, Penfold, Toeniessen, Baerthlein and György, who have been able to show that similar variation also occurs in many other species of bacteria. The variations which have been demonstrated concern not only the power of fermenting particular sugars, but also the habit of capsule-formation, the size, shape and motility of the individual bacilli, the appearance of the bacterial colonies, and, most important from the practical point of view, the virulence towards animals.

The opinion was also generally expressed that these variations in bacteria corresponded to those described in flowering plants by the Dutch botanist De Vries under the term "mutation." It was asserted that bacteria, which were not believed to exhibit sexual reproduction, could not vary on the Mendelian plan, which is characteristically evident in variation following union of gametes.

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It was also shown that the change in sugar reactions followed exposure to the sugar concerned, and was therefore a direct adaptation to environment.

Now in the work which we have been doing in Cheddleton we have been favoured to a high degree by abundance of material, and I think, therefore, that we may claim that we have extended the data, and made more distinct the rules which govern the phenomena.

We have shown (1) that *Bacillus coli communis* can be derived not only from *Bacterium coli mutabile*, but also from *Bacillus paracoli*, and that *Bacterium coli mutabile* can also be derived from *Bacillus paracoli*, the changes occurring in response to changes of environment. Thus an explanation is furnished of our initial problem, *viz.*, the alteration of the intestinal flora in manic-depressive insanity; the non-lactose fermenters increasing in the bowel when the normal chemical conditions therein are disturbed, probably by an increase of protein content; and the lactose fermenters returning when conditions revert to normal, with an increase of assimilable sugar. This observation furnishes a guide to treatment by the avoidance of meat in the diet, and by a plentiful supply of fresh milk and of carbohydrates.

(2) We have been able to show that in the colon and dysentery groups any given individual race may be modified almost at will by exposure to various sugars, in respect not only of sugar fermentation, but of capsulation and other characters.

(3) As the result of these extended observations we have demonstrated that variation does not occur in one mode only, but in two. That one of these modes corresponds exactly with mutation of De Vries, and the other with Mendelian variation.

It will be well at this point to discuss the nature of these two processes. We will begin with the phenomena as found in higher plants and animals, and then pass to those occurring in bacteria, and the interpretation which we wish to place on the latter.

Both mutation and Mendelian variation are examples of discontinuity in the inheritance of characters, the parent giving rise to a descendant which differs from it radically in some respect. Mutation is such discontinuous variation occurring in the descendants of a pure non-hybrid form, it therefore occurs infrequently and irregularly, and it is not possible to predict the moment when it will occur, nor is it possible to predict what the nature of the change will be, since the stimulus determining the change, even if suspected, is so complex that its effect on the equally complex organism cannot be anticipated.

Mendelian variation, on the other hand, consists essentially in the separation of the two different elements (allelomorphs) composing

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a hybrid; it occurs regularly in every generation, and it is possible to predict not only the nature of the descendants, but the numerical proportions in which they will appear: out of every four descendants, one will resemble one grandparent, one will resemble the other grandparent, and two will resemble the parent.

It should be noted that in multicellular plants and animals a variation to be hereditary must have taken origin in the germ-plasm, and therefore cannot result from an external stimulus, which affects only the soma of the parent.

In flowering plants instances of mutation are to be found in the origin of the cultivated varieties of the sweet pea, plants bearing new types of flower arising to all appearance spontaneously from old-established parents. Both old and new types breed true and are therefore pure.

The classical example of Mendelian variation following sexual reproduction occurs in the hybrid between the tall and dwarf varieties of edible pea. This hybrid is as tall as the pure tall since the tall factor is dominant to the dwarf. If two such hybrids are crossed the resulting generation consists of three types—pure tall, pure dwarf, and impure or hybrid tall.

Little attention has hitherto been paid to Mendelian variation in asexual cell division, but Bateson explains as a Mendelian phenomenon the occasional and rare growth of nectarines on peach trees. He considers that the peach tree is essentially a hybrid, in which the hoary character of the peach is dominant to the glabrous character of the nectarine, and that segregation of the peach and nectarine characters can take place in somatic cell division.

In our study of the intestinal bacteria we have found examples of variation which undoubtedly correspond to mutation in higher plants. A race which consistently breeds true under all ordinary circumstances may be assumed to be pure. Now if such a race is exposed to a definite external stimulus for a period prolonged over months, it may form a variant sub-race; for example a paracolon bacillus will not ferment lactose, nor will it give rise to descendants which do so in the ordinary cultures employed in bacteriology, but if it is grown in one lactose culture for several months it may give rise to a lactose fermenting sub-race, which will develop, and continue to grow, alongside the non-lactose fermenting parent race. This is an example of mutation, of the breaking-up of the pure race by a very prolonged, insistent external stimulus. The change is a direct adaptation to the external stimulus presented, and is heritable, because the organism is unicellular, and is not differentiated into somatoplasm and germ-plasm.

On the other hand, consider the case of the variable bacteria, of

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which *Bacterium coli mutabile* is the type. This organism does not itself ferment lactose, but if it is grown on a medium containing this sugar, it will always, and within twenty-four or forty-eight hours, form two descendant sub-races, (1) a lactose fermenter which breeds true, and (2) a non-lactose fermenter like the parent, which again gives offspring of the two types. I would suggest that there is only one theory which will account for the regularity of this recurring phenomenon, namely, that the parent form is impure or hybrid. We are here dealing with Mendelian variation modified by the fact that the segregation of the two characters composing the hybrid is occasioned, not by gametic division, but by an external stimulus. This theory is supported by a further observation—that occasionally and somewhat rarely a third descendant sub-race appears, namely (3) a non-lactose fermenter which breeds true, and is therefore pure. This third sub-race completes the Mendelian scheme as it occurs after sexual reproduction.

If, then, we admit that the variable bacteria are hybrid or heterozygous, and if conjugation does not occur in bacteria, how can this hybrid arise? Our results point to the following explanation: that it arises by mutation of De Vries from a pure form, and that the mutation does not affect the entire constitution of the organism, but only one half of it; in Mendelian terminology only one member of a pair of allelomorphs is affected, so that the descendant is one half variant and one half parental—in other words hybrid or heterozygous.

It has been shown by previous workers, and we have been able fully to confirm the opinion, that these variations occur only in adaptation to the stimulus presented. A bacterial race which does not ferment a particular sugar will form a descendant sub-race which does so only if grown on the particular sugar concerned. This descendant sub-race, however, will retain the power acquired, even if grown for prolonged periods on media containing other sugars or no sugar at all. We have thus arrived at an hypothesis of the greatest importance to the theory of evolution, namely, that a race can adapt itself by variation directly to its environment, and that such an adaptation once achieved is rigorously inherited. This hypothesis is supported by many observations concerning acquired virulence, of which we may instance the work of Toeniessen on Friedländer's bacillus, and of MacGowan and Chung Yik Wang on the organism of hæmorrhagic septicæmia. These observations show that virulence to the tissues of a host is acquired in the same manner as behaviour to a particular sugar.

Such an acquired character is inherited only by unicellular organisms; in higher forms it would, as far as our present knowledge

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takes us, affect the soma only, and not the germ-plasm, and would therefore not be inherited. From the study of acquired immunity we may, however, gather evidence that variation of this nature occurs in the tissues of higher animals; that the defensive cells of the body may, in response to infection, undergo Mendelian variation by which they become virulent to the invading microbe; in fact they may behave as if they were independent unicellular organisms varying in asexual multiplication.

Variation in tissue-cells, although it must involve adaptation for the cell which varies, need not be favourable to the remainder of the body. It is clearly a necessary condition for the evolution of multicellular from unicellular beings, that the cells should acquire a factor inhibiting them from antisocial attacks upon their fellows. Inhibitory factors or chalones become exhausted in old age; horn-less breeds of cattle, in which the development of horns is prevented by an inhibitory factor, "acquire as they grow old small horns"; old women, from exhaustion of ovarian internal secretion, become hirsute like men. This exhaustion predisposes to mutation by which the weakened factors are entirely lost; we have seen that in bacteria mutation occurs in senile cultures; "Professor Chapman states that he has often seen in Virginia very old peach trees bearing nectarines." The factors for the social inhibition of the tissue-cells are also weakened by advancing years; a local irritant acting over a prolonged period will cause the destruction of many cells; this cytolysis will provide a stimulus to the strongest cells which remain in the area irritated, a stimulus well adapted to cause mutation, by which a daughter cell race will arise lacking the social inhibitory factor, capable of invading its surroundings—in fact malignant or cancerous.

In concluding I wish to express my indebtedness to Mr. W. F. Gifford, Senior Assistant in this Laboratory, for his co-operation during the past two years.

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