THE PART OF HEREDITY IN THE ETIOLOGY OF MENTAL DISEASE.

Lastly, from a practical consideration of the subject of insanity, it is very necessary to recognize that the germ cells of every person who is certified as insane and sent to a mental hospital are not necessarily possible potential transmitters of a mental disease. General paralysis of the insane and many other microbial infections leading to disordered mental functions are acquired diseases and are not hereditary. Neither is it right to assume that simple senile decay affecting the brain is transmissible, yet a large percentage of inmates of asylums are sent there on account of senility. These legal administrative conceptions of mental disease must therefore vitiate all statistics in respect to heredity as a cause of mental diseases, because based upon data in which admissions to a mental hospital are in many instances the sole evidence. This does not apply to the same extent to carefully recorded pedigrees; but even these are not free from error, for often all the information that can be obtained is that one or more members of the stock had been in an asylum.

How is the public to know the difference between an inborn tendency to insanity *ab initio* in the ovum, true heredity, and a condition which may arise after conjugation of the male and female germs while the developing embryo is still in the body of the mother? As Sir Bryan Donkin pointed out, congenital disease was confounded with hereditary disease even by medical witnesses who gave evidence before the Royal Commission on Feeble-mindedness. The term "hereditary syphilis" is a misnomer. Much may happen while the embryo is still *in utero*. The normal biological processes of nutrition of the developing embryo may fail; abnormal mechanical conditions may arise in the uterus, interfering with the proper development of the embryo; or mechanical conditions in the process of development of the embryo may arise, interfering with the development of structure. Of all the structures in the body of the embryo likely to be affected by a departure from normal dynamic biological conditions of growth, the great brain or cerebrum is the most likely. The neo-encephalon—new brain—of mammals appears first as two hollow buds from the telencephalon, which by rapid cellular proliferation grow upwards and backwards to cover up completely the basal ganglia and mid-brain to form the cerebral hemispheres. In that process many mechanical failures and accidents may occur, interfering with the vascular supply, or nutrition of the rapidly proliferating cells, whereby the process may be arrested altogether, as in anencephaly, or partially arrested, as in the brain of the idiot or low-grade imbecile. There is evidence of a possible vascular cause through a lack of correspondence in the normal rate of growth of the dura mater and soft membranes and the growth of the brain. Owing to this the veins enter the longitudinal sinus in a direction opposite to the current of the blood stream in the frontal lobes—an anatomical condition which favours venous stasis. This I have put forward as an explanation of the fact that the frontal lobes are the seat of early and most pronounced meningo-encephalitis and atrophy in paralytic dementia, because the spirochaetes, being anaerobic, would develop more easily where there is venous stasis. Again, prolonged labour and difficulties in delivery requiring the use of instruments may be responsible for injury of the brain.

Idiots and imbeciles occur in all grades of society (frequently they are the first-born), and it is not at all uncommon to find nothing in the paternal or maternal family history—even when a pedigree can be obtained of three or four generations—to account for this pronounced failure of development of the anatomical basis of mind. The late Dr. Ashby considered that 25 per cent. of the cases of idiocy and imbecility were due to causes other than heredity.

I feel that the subject is one which still requires an enormous amount of patient investigation before any definite conclusions can be arrived at, and I am more than ever convinced of the wisdom of what Harvey's great contemporary Bacon said in his *Advancement of Learning, Divine and Human*, when he wrote: "First, therefore, in this, as in all things which are practical, we ought to cast up our account, what is in our power, and what not; for the one may be dealt with by way of *alteration*, but the other

by way of *application* only. The husbandman cannot command, neither the nature of the earth nor the seasons of the weather; no more can the physician the constitution of the patient, nor the variety of accidents. So, in the culture and cure of the mind of man, two things are without our command—points of nature, and points of fortune."

Remarks

ON

SENSITIZATION AND DESENSITIZATION IN SKIN DISEASE.*

BY

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DISEASES of the skin may be divided for certain purposes into two groups—the first, where the cutaneous manifestations can be shown to be the direct result of the presence in the skin of a specific parasite, as in tuberculosis, syphilis, and scabies; and the second, where the eruption is the manifestation of a reaction to some process which may not have been adequately explained. In the first or parasitic group, because we possess a precise knowledge of the nature of the condition, we can often cure the disease by methods of treatment having as their object the destruction of the causal parasite. This does not apply to the second group, where we may only be dealing with a symptom, as in the case of eczema, urticaria, and other conditions; where, although the local treatment is often successful in removing the eruption, it does not necessarily cure the condition—using the term "cure" in its strict sense—because the factors bringing about the dermatosis may be uninfluenced by the remedies used. This treatment of a symptom is not confined to dermatology, for there are many other complaints, both medical and surgical, where the same method is adopted. Even in cancer,† to take what may be an extreme case, when the surgeon takes away with the knife the primary tumour, and so far as possible any other structures liable to contamination, the highly developed operative technique only removes the result of some mysterious agency, not the cause, for the cause of cancer is still an unsolved riddle. While the discovery of the pathogenetic bacteria made clear the nature of the first or infective group of skin diseases, it left, in the main, the second or symptomatic group unexplained. The doctrine of sensitization offers a possible solution to some at least of these conditions.

The Theory of Sensitization and its Applications.

The theory of sensitization is based upon the early experiments of Richet, who, in 1902, demonstrated that when an animal is injected with certain proteins it develops a peculiar sensitiveness to subsequent and often very small doses of the same agent or antigen. The reaction following the second injection has been termed the anaphylactic shock, and may include a general disturbance besides cutaneous phenomena, as in some of the forms of serum sickness occasionally met with following the use of an antitoxin. It is now known that a great variety of different agents can act as sensitizing antigens—vegetable and animal proteins, bacterial products, and even drugs. A number of cutaneous eruptions appear to be attributable to this state of sensitization, and this theory of origin has in particular been applied to certain forms of eczema, urticaria, general pruritus, certain erythemas, and possibly other conditions, such as dermatitis herpetiformis. It may seem a long cry from the violent reactions observed in serum sickness to the relatively quiet efflorescences of eczema and the other diseases catalogued above, but there is nevertheless a considerable body of evidence in favour of the view that the eruptions are the result of a special sensitization of the skin. With the object of avoiding a possible source of confusion two preliminary observations may be made.

* Abstract of address given to the South Essex Division of the British Medical Association.

† This paper was written some time before Dr. Gye and Mr. Barnard had published the results of their researches.

In the first place, the names we attach to the various dermatoses may not designate specific diseases, but possibly only reactions arising from more than one cause, and this quality must obviously make the investigation of any one of them the more difficult. This statement is illustrated by consideration of the condition termed "dysidrotic eczema, or dysidrosis," recognized by an eruption of deeply seated vesicles affecting both hands, the fingers especially, and sometimes also the feet. It prevails in spring and summer, and this and the tendency to relapse at the same period of each year has led to the belief that sunlight has a direct effect in bringing about the eruption. Dysidrosis is placed by many observers within the eczema group by reason both of its clinical and histological features. It would therefore appear to belong to the class of diseases which may be attributable to sensitization. Research, however, has shown that certain forms are of parasitic origin and due to the invasion of the skin by one of the ringworm fungi, as in the following case.

The patient, a man aged 33 years, came under observation in April, 1923. He had first suffered from the condition complained of in 1920, the eruption then attacking the hands and the feet. During the whole of 1921 he remained free, but was again affected in the following year. When seen in April his condition might be described as the classical form of dysidrosis. As a routine measure the epidermic covering of some of the vesicles was removed with a curette and examined microscopically, and in the specimens thus prepared an abundant ringworm fungus was detected.

Darier,¹ writing on this subject, states that in 80 per cent. of the cases presenting the features of dysidrosis it is possible to discover a mycelium in the squames, or in the roof of the vesicles, but he does not deny, and others positively affirm, that there does exist a true dysidrosis, a condition *sui generis*, neither parasitic nor traumatic. In the case recorded above it would have been impossible even for a trained observer to distinguish by simple inspection alone—that is, without the aid of the microscope—between two completely different conditions.

Secondly, it has also to be recognized that although a state of sensitization may be shown to exist it does not necessarily follow that any given eruption is the result of this sensitized state, and two good examples of this circumstance are given by Whitfield² in his Lumleian Lectures. He cites there the case of an infant, aged 3 months, with acute eczema, who was so sensitive to egg that on one occasion, when a small quantity of egg-yolk was included in the food, severe vomiting and diarrhoea resulted, but without in any way affecting the eruption. His second case is similar to the first, for the patient, a child aged 14 months, was also egg-sensitive and also suffered from eczema. When egg was included in the dietary a marked general disturbance followed, with urticaria, but the eczematous eruption remained unaltered. These patients were both sensitized to egg, but in neither case was the eczematous eruption the result of egg-sensitiveness.

To demonstrate that any given eruption is the result of sensitization it is necessary to satisfy two conditions—first, that the patient is sensitized, and secondly, that the eruption is the result of this sensitization. It is not always possible to obtain the complete proof, and, indeed, in a considerable proportion of cases the argument will depend rather upon inference than fact. Sometimes all the conditions can be satisfied, as in the following two cases where the nature of the process and the effects of specific treatment are clearly displayed.

The first is recorded by Widal, Abrami, and Joltrain,³ where a man under their observation became so sensitive to emetine powder that the least contact with it provoked an attack of acute eczema. Knowing the nature of the antigen, these observers were able to desensitize their patient by a series of subcutaneous injections, using at first 1 c.cm. of a solution of emetine 1 in 20,000, the strength being gradually increased. By this means the patient ultimately became completely free of his intolerance to the substance.

The second case was brought under my observation by Dr. Moncrieff when casualty medical officer at the Middlesex Hospital. A medical student working in the dissecting room developed formalin dermatitis of the hands, which interfered with his work and caused him considerable inconvenience. It was decided to attempt specific desensitization, and with this object in view the following

procedure was carried out. On November 29th an injection of 1 c.cm. of a solution of formalin 1 in 1,000,000 was given; a second injection on December 3rd of 2 c.cm. of the same solution caused a flaring up of all the lesions. Further injections were made on December 5th (4 c.cm.), December 12th (0.4 c.cm. of 1 in 100,000 formalin solution), and a final dose of a similar strength on December 18th. The rash had by this time completely disappeared, and the patient was able to resume his work and has had no further recurrence of the eruption.

While these cases illustrate in the most complete manner the relation of the sensitized state to certain forms of eczema, there are other, if less convincing, methods of demonstrating sensitization in many cutaneous diseases. There are, for example, phenomena preceding the cutaneous reaction—including among other things a fall of blood pressure, diminished coagulability of the blood, and leucopenia—termed by Widal the haemoclastic crisis. As these are identical with the changes observed in genuine anaphylactic shock, their detection before the appearance of an eruption may be taken as evidence of a condition of sensitization. This method of proof has been used in a case of urticaria under the observation of Pagniez and Pasteur Vallery-Radot,⁴ the more important feature of which may be summarized as follows.

This particular patient was found to be sensitive both to vegetable and animal albumins, and in his case the haemoclastic crisis could be demonstrated before the urticarial rash appeared. But when aliments were ingested from which the harmful substances had been excluded both the cutaneous reaction and the haemoclastic crisis were wanting, while actually a leucocytosis and raising of the blood pressure occurred, such as would normally be met with during the digestive period. The nature of the eruption being in this manner proved, desensitization was brought about by a remarkably ingenious plan. One hour before his repast the patient was made to consume tiny amounts of the foods composing it; this miniature meal desensitized him, and allowed him to eat subsequently without ill effects.

The protein skin tests have also been used for the purpose of demonstrating sensitization. The technique advocated by Engman and Wander,⁵ which has the advantage over others of avoiding the production of a wheal in urticarial subjects, is as follows: A number of incisions one-eighth of an inch long are made with a sharp von Pirquet knife through the epidermis of the forearm. These are moistened with decinormal caustic soda solution and then the test proteins are applied. A positive reaction consists of a distinct wheal surrounded by an erythematous blush. The well known case of Fox and Fischer⁶ affords striking proof of the practical application of this method. They refer to a man aged 35 years, with chronic eczema of the hands and wrists, who consumed considerable quantities of cabbage, and who, when tested, gave a strong positive cabbage reaction. When this vegetable was excluded from his diet the eczema got well, returning when cabbage was again eaten. He was thus cabbage-sensitive and the eczematous eruption was a manifestation of his sensitized state.

In adopting this method of investigation it is necessary to remember that while an individual may be sensitized to any given protein, it does not necessarily follow that the dermatosis is a consequence; Whitfield's two cases quoted above are striking examples of this fact. The reaction is also open to various interpretations, different observers adopting a different standard of the positive degree. Fox and Fischer appear to have summed up the position in saying that it is difficult at present to draw definite conclusions regarding the true value of the protein skin tests in eczema of adults, and they further add that these tests might prove useful in a small proportion of cases.

Approaching the problem in a novel manner, Cranston Low⁷ has, in a series of convincing personal experiments, investigated the effects of sensitization with *Primula obconica*. Before he began his experiments he was, he states, able to handle the plant, and even rub the leaf on his skin, with impunity. He purposely scarified a small area on the back of the forearm, rubbing in the crushed

leaf and allowing the juice to dry on. The region so treated healed completely, leaving a slight scar, but without itching or dermatitis. Although there was no evidence that anything unusual had taken place, a very definite deviation from the normal actually had occurred—the investigator was now sensitized to *Primula obconica*. The subsequent steps in the experiment are remarkable. Three weeks after the operation recorded above had been carried out the plant juice was applied to the unbroken skin on the same area of the arm, with the result that an acute vesicular dermatitis developed, attaining its maximum in ten days. The sensitization was not a local one, for on rubbing the plant on the other forearm and the thigh, a characteristic reaction, but of lesser degree, was produced. Two years later the sensitized state still persisted, a reaction with the plant being recorded after this interval had elapsed.

The foregoing refers to specific sensitization where the harmful agent can be identified. In these cases specific desensitization can be attempted by administering in various ways minute doses of the causal antigen with the object of "re-educating" the tissues. But the investigator will not always be in so favourable a position, and it will often be found necessary to assume that a state of sensitization exists. An eruption, for example, may be considered to depend upon bacterial sensitization of the skin from a focal infection of the teeth, tonsils, pelvis, or elsewhere, the proof of the relationship between the two depending upon the improvement or disappearance of the eruption when the infected focus is identified and suitably treated. Examples of this relationship may be found in cases of lupus erythematosus and urticaria, where, as Barber⁸ has insisted, focal infection assumes a special importance. The following are examples of such a relationship.

A woman, aged 22, came under observation with typical lupus erythematosus of the hands and feet of six years' duration, which had resisted all the usual methods of treatment. During the course of the disease enlarged axillary glands, considered to be tuberculous, had developed; their removal effected no change in the disease. It was noted that the tonsils were considerably infected, and upon their enucleation the eruption cleared up.

Many dermatologists hold that lupus erythematosus should be included among the tuberculides, a group embracing a variety of dermatoses supposed to be due to the toxins carried by the blood from some distant tuberculous focus—in some cases tubercle bacilli may actually be present in the skin lesion. In this connexion it is interesting to note that Dr. Fordyce⁹ has stated that Dr. Cannon, his assistant, had been carrying on certain investigations in the pathological department of Columbia University, including tissue inoculation from cases of lupus erythematosus into guinea-pigs. Out of thirty cases inoculated, typical tuberculosis developed in five. This does not necessarily disprove the theory of focal infection of the teeth, tonsils, etc.; it implies that some cases of this disease are different from others, and further demonstrates the difficulty of separating apparently similar eruptive types.

Sensitization to bacterial products from a focal infection may sometimes be the cause of chronic urticaria and angio-neurotic oedema, as in the following two cases, similar to those described by Barber.

The first patient, a woman of middle age, had suffered from repeated attacks of giant urticaria over a period of seventeen years, during which time she had hardly ever been free from the eruption. It was discovered that certain of the accessory nasal sinuses were infected, and when these were drained the urticarial manifestations ceased abruptly.

The second case is even more striking, and presents some remarkable features. A woman, aged 34, came to hospital giving a history of giant urticaria extending over five years. A search to discover the cause was at first without definite result, and it was therefore decided to attempt desensitization by injections of whole blood, a method of treatment to which reference will be made later. She received seven injections, with the result that the eruption during the treatment became less and less pronounced, and finally entirely disappeared. As during the whole course of her illness she had never been free from some degree of urticaria for more than a few days, the hope that she had been cured was entertained. It was therefore extremely disappointing to find, six weeks after the injections had been discontinued, a return of the eruption in a severe form. Further investigation showed that one antrum was infected, the purulent contents being of an extremely offensive character. Suitable treatment of this focus resulted in what appears to be final cure.

This case shows the importance of a complete investigation in cases of urticaria; it also demonstrates that a non-specific method of treatment can exercise a real control over disease even when the cause remains operative.

Utilization of the Theory in Treatment.

The theories of sensitization would have little more than academic interest were it not possible to utilize in treatment methods of desensitization based upon them. These may be divided into two groups—specific and non-specific.

Specific desensitization may be undertaken by giving the sensitized individual a series of doses of the known harmful substance, beginning with very small amounts, which are gradually increased until ultimately a state of tolerance is acquired. While this is the more scientific method, the most extensive investigations often fail to reveal the nature or source of the offending agent, and it may be necessary to adopt the second form of treatment—one that has been criticized as empirical, and has been termed from its nature non-specific. This procedure assumes various forms, two of which may be adverted to here.

Non-specific desensitization may be brought about by the comparatively simple method of intravenous injections of physiological salt solution. Some observers attribute the results obtained to the contamination of the solution with air-borne bacteria, and believe that little or no effect follows the use of a solution from which bacteria and their products have been excluded, or removed by double distillation. There would appear to be some reason for this belief, and in the case quoted below the fluid was purposely allowed to become contaminated before sterilization for use.

The patient was a married woman, aged 36, suffering from multiple arthritis and lupus erythematosus. No focus of infection could be detected in the teeth, tonsils, or elsewhere, and she appeared to be free from any tuberculous taint. As the condition had failed to respond to a variety of local applications, it was decided to attempt to desensitize her by intravenous injections of saline. The first injection of the series, amounting to 50 c.cm., was administered on September 3rd; in all, five injections were given, at intervals of seven days, in increasing quantities up to 200 c.cm. Following the first, the severe pains in the joints, which had been of such a character as to interfere with sleep, entirely disappeared. The eruption steadily improved, and although it was not completely removed it became of relatively slight degree. The injections were well tolerated and were followed by a moderate febrile reaction, excepting the last, which caused the temperature to rise to 101°.

Injections of Whole Blood.

Injections of whole blood—a method largely employed on the Continent, but apparently only used to a limited extent in this country—are often brilliantly successful. Auto-haemotherapy owes its place in dermatology to Ravaut, who, in 1913, called attention to it and to the conditions in which it might be employed. The technique used by different investigators is not always the same; the following method appears to give satisfactory results and has been adopted in the various cases recorded below.

From a vein in the arm 5 c.cm. of blood is withdrawn into a syringe and immediately injected deeply into the muscle high up in the buttock region in the position usually selected for intramuscular injections in this situation. It is important so to prepare the patient that no undue delay takes place between the withdrawal of the blood and its re-injection. If this be neglected the practitioner may find himself in the embarrassing position of having allowed the blood to clot in the syringe and being thereby prevented from completing the operation. If this precaution be taken there is little else, apart from the usual aseptic regime, that need be observed, for the procedure would seem to be attended by little discomfort to the patient and to cause only in the rarest cases any subsequent disturbance. I have once met with fever following the injection, and once with severe urticaria. The application of the method will best be illustrated by the following series of cases:

Case 1.—A female patient, aged 75, with severe dermatitis herpetiformis of fifteen months' duration. The nature of the case was manifest from the type of the eruption, its distribution including the mucous membrane of the mouth, and from the marked eosinophilia. Treatment with whole-blood injections was commenced in September, 1923, and in all seven injections were given at weekly intervals. As a result the eruption cleared up and the patient seems to have made a satisfactory recovery. A certain amount of local treatment was carried out at the same time, but in view of the duration of the complaint before the special method was undertaken and of the kind of treatment that had been

employed in this period, it may reasonably be assumed that the result should be attributed to the blood injections.

Case 2.—A male patient, aged 53, with chronic eczema of the hands and forearms, existing from early childhood. Almost every recognized application had been used, with never more than temporary success. It was suggested to the practitioner in charge of the case that he should try the effect of a series of whole-blood injections. Rapid improvement followed, the patient in describing the result stating that his hands, which had been severely affected, became "like velvet."

Case 3.—This case was also an example of eczema involving the face, with considerable oedema. The condition had existed on and off for one year, and when seen a severe and acute phase had been in progress during three months. Various methods of treatment, such as dieting and local applications, had been employed without success. Following a series of whole-blood injections the eruption completely cleared up.

Some of the most striking results following the administration of whole blood have been met with in urticaria, general pruritus, and especially in furunculosis. The following cases may be cited as examples of the application of this method in these conditions.

Case 4.—A young male who had suffered from chronic furunculosis extending over about three and a half years. He had been treated with vaccines, colloidal manganese, and in other ways, but without benefit. He was put on injections of whole blood, and immediately began to improve. After several injections he ceased attending hospital, so that his complete history is unknown. As he was most enthusiastic about the treatment and as it inconvenienced him in no way, this may be taken to mean that he has been cured, for he was completely relieved towards the end of the period during which he remained under observation.

Case 5 is somewhat similar. The patient, a woman aged 23, had suffered from a succession of boils during two months. She was given five injections of her own blood. Improvement began at once, and at the termination of treatment she became, and has remained, free from the complaint.

The next three cases to be recorded are examples of the results of this method of desensitization in general pruritus, a condition in which whole-blood injections seem to have a special use. It will be noted that in all the itching had been in existence for a considerable time, and that the benefit appeared to follow directly upon the injection.

Case 6.—An example of severe general itching in a woman aged 45. This had been present for three years and had at one time undergone temporary improvement following the extraction of some teeth. The skin was extensively scratched, with, in consequence, some degree of secondary pyoderma and lichenization. There was a history of wheals, but these were never seen on the occasions when the patient was examined. In all, six injections of whole blood were given. The itching entirely ceased, and, no doubt in consequence of this, both the pyoderma and lichenization disappeared.

Case 7.—A woman with severe pruritus and an indefinite history of urticaria of two years' duration. This patient gave a history of three attacks of food poisoning, and as she appeared to have had colitis a vaccine made from the intestinal flora had been used for some time, but without effect. On April 20th, 1923, she was given an injection of her own blood, following which the itching almost entirely ceased. Subsequently three other injections were given, with the result that the patient has remained free from the pruritus.

Case 8.—A man, aged 64, came to the skin department of the Middlesex Hospital in December, 1923, complaining of severe general pruritus of two years' duration. The skin was observed to be generally markedly infiltrated, the lymphatic glands in the axillae, groins, supraclavicular regions, and on the lateral aspects of the thorax were enlarged and prominent, so much so that Hodgkin's disease was suspected. The blood count was as follows: haemoglobin 82 per cent., red blood cells 4,800,000, white blood cells 12,800; differential count: polymorphonuclears 77 per cent., lymphocytes 11 per cent., mononuclears 10 per cent., and eosinophils 2 per cent. One of the glands was removed for microscopic examination and presented the following features. The lymphoid tissue was generally reduced; there was increase of the reticular elements, but no giant cells were found present. This patient was taken into the hospital, and while there four injections of whole blood were given. These were well tolerated, except the third, following which there was a considerable and prolonged febrile reaction. The result of treatment in this case was striking. The skin gradually became soft and pliable, the glands disappeared, the patient entirely lost all itching sensation, and made a complete and satisfactory recovery.

When we undertake a form of specific desensitization we are, as the facts above demonstrate, in a secure position; but it is not so evident that our methods are of equal scientific precision when one of the non-specific methods is employed. The proof of the nature of the condition would then seem largely to rest upon the results of treatment, the argument being that because the condition for which treatment was undertaken gets well or improves, a desensitizing method having been used, therefore we have been treating a patient who has been sensitized, although the nature of the sensitizing agent or agents remains unknown. But even if we accept this position, admittedly an unconvincing one, we can still point to results obtained which must be satis-

factory both to the patient and the practitioner, whether we label them with a special name or not. The method, like others, has a limited application, but within those limits it would seem to have a distinct value and position in therapeutics.

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BIOCHEMICAL CHARACTERS OF CERTAIN BACTERIA

WHEN LIVING IN ASSOCIATION OR ARTIFICIALLY MIXED,
AND WHEN LIVING SEPARATELY.

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SOME years ago I noted that when two species of bacteria are living together in symbiosis, or close association, or are artificially mixed, the symbiotic or mixed cultures may present certain biochemical characters which neither species possesses when grown separately. I will limit myself in this paper to touching upon the changes in fermentative properties, quoting only a few examples. The results of the complete investigation will be published at a later date in a more complete paper.

Bacteria Used.

The bacteria I have used in my experiments are: *Bacillus typhosus*, *Bacillus morgani* (Morgan's bacillus No. 1), *Bacillus dysenteriae* Flexner, *Bacillus proteus*.

The strain of *B. typhosus* was isolated from a case of typhoid fever, and shows all the typical serological reactions and biochemical characteristics of the typhoid bacillus; it is very highly agglutinated by typhoid serum; it does not produce gas in any carbohydrate; it produces acidity in glucose, levulose, maltose, galactose, mannitol, dextrin, and sorbite.

The strain of *B. morgani* was isolated from a stool; it is motile; it produces acidity and gas in glucose, levulose, and galactose, but neither acidity nor gas in any other sugar. In this paper I will refer to it as Strain S.

The strain of *B. dysenteriae* Flexner is serologically and biochemically typical; it produces acidity in mannitol. It was obtained from the Lister Institute.

The strain of *B. proteus* was isolated from a case of enteritis; it is motile and liquefies gelatin and serum rapidly; it produces acidity and gas in glucose, levulose, galactose, saccharose, and glycerol; it produces neither acidity nor gas in lactose, dulcitol, mannitol, maltose, dextrin, adonite, inulin, sorbite, inositol, salicin, amygdalin, isodulcitol, or erythrite. As I have stated in other publications, the term *proteus* covers a group of closely allied bacilli and not one species only. The strain I have used is very similar to the variety which I called *paradiffuens* (see Castellani and Chalmers's *Manual of Tropical Medicine*, p. 943). In this paper I will denote it as *B. proteus* (P).

B. typhosus + *B. morgani*.

Action on Maltose.—*B. typhosus*, as is well known, does not produce gas in maltose or any other sugar, only acidity. *B. morgani* (Strain S) has no action whatever on maltose; it produces neither acidity nor gas. Maltose peptone water tubes inoculated with *B. typhosus* alone or *B. morgani* alone and kept in the incubator for as long as a month never show production of gas. One would expect, therefore, that the mixture *B. typhosus* + *B. morgani* would not cause production of gas in maltose, but it is not so. If a tube of maltose peptone water is inoculated with *B. typhosus* and immediately after with *B. morgani* and placed in the incubator at 35° C. for forty-eight

1, Maltose peptone water tube inoculated with *B. typhosus*; gas absent. 2, Maltose peptone water tube inoculated with *B. morgani*; gas absent. 3, Maltose peptone water tube inoculated with *B. typhosus* + *B. morgani*; gas present.