Excision of the Head of the Femur.

I now come to the operation which has engaged my special attention for some time past. Excision of the hip-joint or excision of the head of the femur has for a long time been one of the standard operations of surgery for many affections. Of late years it has fallen into disrepute, and deservedly so, for as performed in the old manner with complete lack of correct after-treatment the usual end-result was an unstable pathological dislocation. The operation flourished in the surgical epoch of excision of joints when surgeons were primarily concerned with the eradication of disease and operations were less commonly conceived in terms of function. The operation here designated "excision of the head of the femur," as applied to osteo-arthritis of the hip-joint and carried out in the manner to be described, is a somewhat different proceeding. It is fundamentally reconstructive, and not destructive, in type.

In brief, the operation involves the following steps: (a) The removal of the overhanging mushroomed portion of the femoral head, leaving the stump of the neck of a reasonable length and with a slightly expanded upper end rounded off so as to simulate a new head; (b) the stump of the neck is brought deeply into the acetabulum by fully abducting the limb; (c) the great trochanter, which has been detached as an integral step in the exposure of the hip-joint, is re-attached to the femoral shaft at a lower level, thus acquiring a position of mechanical advantage (Figs. 1 and 2). This latter manoeuvre is an important feature of the operation. I have used it only in my later operations and before I was aware that it had been already introduced by Royal Whitman of New York as part of his reconstructive operation on the hip for old fractures of the neck of the femur. There are other technical details of importance and interest. In removing the femoral head it is necessary to use a wide osteotomy with a curved shaft in order to reproduce the rounded stump of the neck. The surface of the cancellous tissue thus exposed, after being smoothed off by filing, is thoroughly impregnated with Horsley's wax. The same procedure is carried out in the raw area left by the detachment of the trochanter. In addition, this latter area is covered by a small aponeurotic flap elevated from the vastus externus and turned upwards, leaving bare the femur in the region where the trochanter is to find its new site. With regard to the approach to the hip-joint used in this operation, in my experience the posterolateral route described by Brackett² is of all methods the most adequate.

After the operation the patient is nursed for six weeks on an abduction frame; the hip is completely immobilized by means of a fixed extension for the first three weeks only; after that gentle massage and active movements through a small range are given each day. In the intervals of treatment the patient is encouraged to repeat the attempts at active movement, the foot now being anchored to the lower part of the frame by a slack clove-hitch bandage. At the expiration of the six weeks' recumbency, if the patient has moved the hip with fair comfort (and this is usual), a calliper walking splint is applied and he is allowed to get up on crutches. A few weeks later full weight is borne on the calliper ring and the crutches discarded. The physiotherapeutic treatment is continued for some months, and the calliper splint is retained for at least six months; but in my experience the hip-joint is stable after three months, and the natural tendency of the patient is to discard the calliper at an early date.

The operation here described has given me exceedingly gratifying results, and for this reason has been described in some detail. I believe that it is applicable for the relief of the pain or malposition in moderately advanced cases of osteo-arthritis of the hip-joint at any age, provided the patient is constitutionally fit to undergo a major operation. There are few mechanical difficulties in the way of its fairly rapid performance; it takes less time and is less provocative of shock than an efficiently carried out arthrodesis. It is thus specially suitable for older patients, but my own trend at the present time is in favour of utilizing it also as an alternative to arthrodesis in younger individuals. The operation appears to give complete relief from the intolerable pain, and it also ensures the correction of the malposition. The degree of mobility in the reconstructed joint varies in different cases and under the influence of many factors. To some extent the range of mobility depends on the amount of bone removed in the resection of the femoral head—a factor which, as is well known, so often determines the function of any joint excision or arthroplasty. In a few individuals the range of

mobility, which is free in the early days after the operation, later diminishes very considerably, but this, happily, is not associated with any return of the old pain and discomfort.

It is not suggested that this operation is in any way original either in its conception or its application, but a somewhat intimate acquaintance with the technicalities involved in its performance and personal experience of its effectiveness have urged me to emphasize its place in the repertoire of surgical procedures available for osteo-arthritis of the hip-joint.

REFERENCES.

¹ *Acta Med. Scandinavica*, 1921, vol. lv, fasc. ii. ² *Boston Med. and Surg. Journ.*, February 5th, 1912.

THE ETIOLOGY AND TREATMENT OF DIABETES:

WITH SPECIAL REFERENCE TO THE SIGNIFICANCE OF A STARCH-SPLITTING AND ACETONE-FORMING ORGANISM FOUND IN THE STOOLS OF DIABETIC PATIENTS.

BY

ARNOLD RENSHAW, M.D.LOND., D.P.H.,

LECTURER IN PATHOLOGY, MANCHESTER UNIVERSITY; BACTERIOLOGIST,
ROYAL EYE HOSPITAL, MANCHESTER; AND HONORARY PATHOLOGIST,
ANCOATS HOSPITAL, MANCHESTER;

AND

THOMAS H. FAIRBROTHER, M.Sc.VICT.

In the consideration of the pathology of diabetes very little is known concerning the source of the acetone bodies—acetone, diacetic acid, and beta oxybutyric acid—which are eliminated from the body in this disease, and which are considered to be the cause of the acidosis and coma which result from their accumulation. The generally accepted view is that these bodies are derived from the amino-acids of the protein molecule, from the fats of the tissues, or even from carbohydrates, but the tendency is rather to explain their origin from the oxybutyric acid derived from fats.

In other words, there is general confusion on this point, and Adami correctly focuses present-day knowledge concerning them when he says, "we cannot as yet say definitely what is the origin of these bodies, whether from the amino-acids of the protein molecule, from the fatty acids, or from the carbohydrates." No one has, so far as is known, laid down any experimental proof that these bodies may be derived from the carbohydrates by bacterial action within the alimentary canal.

Bacteria capable of producing acetone from starch or other carbohydrates have been known to exist for some time; thus in 1905 Schardinger¹ first described such organisms. Secondly, under the name of "Amylobacter," Bredemann,² in 1909, described acetone-producing bacteria possessing spores. In this country attention was called to the practical application of these bacteria to industry by Fernbach and Strange³ (Eng. Pat., 1912, No. 21,073), who actually manufactured acetone on the commercial scale by the ferment action produced by those bacteria on starchy foods.

It is known that the acetone production from starch is not restricted to the action of one particular bacterium, but it is very likely that there exists a family of the bacteria which have been described generically as "Amylobacter." The difference between the members of the family is not completely understood yet, but there are distinct differences in size—particularly in the width of the different organisms. Chemically, the point of similarity seems to be acetone production, which is common to all, and the point of difference the nature of the alcohol produced along with the acetone. Thus Fernbach's organism produces acetone and butyl alcohol, and this was developed during the war by Dr. Weizmann on account of the value of these two products, the one as a solvent for gun-cotton, and the latter for its use in connexion with isoprene, an intermediate body in the synthesis of india-rubber. In addition to this there is a complete description in the literature of another organism, *B. acetoehtylicum*, described by Northup, Ashe, and Senior.⁴ This organism produces 10 per cent. acetone and 25 per cent. ethyl alcohol and small quantities of propyl and butyl alcohol. It is a much thinner organism than the one described by Fernbach, being only 0.2 to 0.3 μ against 0.8 to 1.0 μ .

A description of the acetone-butyl alcohol fermentation from starch and its technical application is given by Gill⁵ and a description of the organism was published by Thaysen⁶ in

1921. The attention of the authors was drawn to this process in 1919, and the similarity of the products formed by it with those found in diabetes at once suggested to them the possibility of the organism being connected with this disease. Two differences were noted: in diabetes glucose was also present in the urine in addition to the acetone bodies; and in the case of the organism the result of fermentation yielded also butyl alcohol.

It appeared probable, however, that the products of such a fermentation in the alimentary canal by this or a similar organism might upset the glycogenic function of the liver, resulting in the excessive accumulation of glucose in the blood, with a consequent overflow elimination by the kidneys as soon as the blood sugar content became too high. It was further highly probable that the butyl alcohol or other alcohol formed during the course of such a fermentation could be oxidized in the liver so as to avoid elimination as such by the kidneys. This substance might, in fact, be the cause of the pigmentary cirrhosis of the liver sometimes met with in diabetes. It was resolved therefore to examine the stools of diabetic patients for the presence of an acetone-producing organism of the *Amylobacter* group, and attempts were begun in 1919 to isolate such a bacillus and to obtain ultimately a typical acetone fermentation therefrom. At the time these experiments were started very little information was available to the authors regarding methods of cultivating the organism, and successive publications had to be studied to glean a knowledge of the conditions required for a typical fermentation to be carried to a successful completion. The presence of such an organism in the stools of diabetic patients was quickly detected, and this organism produced a certain amount of gas and set up a fermentation in starch media. Films of these cultures showed the presence of a spore-forming bacillus very similar to the organism described as *B. amylobacter* by Fernbach, and described by Gill in 1919. A recent case of diabetes in a very young girl presented a very favourable opportunity for obtaining such organisms in greater numbers than were obtainable in older patients where the disease is of more chronic type.

The results of the present investigations show that in each of five cases we have isolated from the stools of diabetic patients an organism which is capable of producing acetone, *N* butyl alcohol, beta oxybutyric acid, and diacetic acid. The acetone and alcohol are present, as will be seen, in large quantity in good fermentations. Further, an analysis of the stools of these patients has been made and acetone has been recovered from the stools to a certain extent.

In view of the ready absorption of acetone by the blood, the full fermentation yield of acetone cannot be expected in the stool as passed per rectum; but the presence of this substance in the stool, together with the presence of an acetone-producing organism, would point to the alimentary canal as the source of intoxication in diabetes. This fact is significant when it is remembered that the organism flourishes best in carbohydrate media, and that carbohydrate foods are contra-indicated in diabetes. The further description can best be considered as follows:

Methods and Media Used.

The following media were used:

Culture Medium A (Semifluid).—Quantities: Ground rice 54 grams, fine oatmeal 6 grams, water to make 1,000 c.cm. The rice and oatmeal are fed slowly into warm water with good stirring. Care should be taken to avoid lumps. Bring to the boil and keep at the boil for a short time to ensure that the starch is gelatinized. Make up to volume and tube out. Sterilize for two hours at 30 lb. pressure.

Alternative Medium (Semifluid).—Quantities: Ground maize 60 grams, made up to 1,000 c.cm. of mash with water. The method of making up is the same as above. The important part is to have the material finely ground and to see that the mash is perfectly homogeneous, otherwise sterilization is difficult. For weaker strains better progress may be made with a 4 or 5 per cent. mash made up in the same way.

Culture Medium B (Solid).—First make up 1,000 c.cm. wort. Mash 100 grams of finely ground maize (or 90 grams of ground rice and 10 grams of oatmeal) with water to make up 1,000 c.cm. After boiling for fifteen minutes cool to 60° C. Add 10 grams of ground malt and keep at 60° C. for one hour, stirring all the time. Then bring to the boil for fifteen minutes to kill the diastase. To this add 10 grams of gelatin, 10 grams of calcium carbonate, and 20 grams of agar. Heat gently to bring these into solution, then filter. Tube out and sterilize for one hour at 15 lb. pressure.

Method of Isolation.

The stool from the patient is emulsified with sterile water or saline. If two or three days old this emulsion will contain spores,

and it can be pasteurized for fifteen minutes at 75° C. before inoculating into Medium A. If fresh, it is preferable to inoculate direct without pasteurizing. In any case heavy inoculations of the stool should be made by means of a sterile pipette to the bottom of the tube containing Medium A. These are then incubated for one to three days. Gassing may or may not result, but the medium should become rather more liquid even in impure cultures. Spores will now have formed, and pasteurization may be carried out for ten to twenty minutes, at 75° to 80° C., when portions of the culture are diluted in sterile saline. It is preferable now to mix them in culture Medium B so as to isolate separate colonies. This medium should be melted and then cooled to 42° C. before admixture of the diluted pasteurized growth from the previous incubation, the medium being poured before solidification into sterile glass tubes 6 by 1 fitted at each end with sterile rubber stoppers. (These tubes should have been plugged with wool at each end and sterilized, the stoppers having been autoclaved.)

When solidified the inoculated tubes are incubated until growth occurs and the medium is split by the gas formation, which occurs round the colonies of the acetone-producing organisms or other bacteria. The tube is then uncorked at one end, warmed to allow the solid medium to slide out into sterile Petri dishes, and then cut up into slices, scrapings obtained from the different colonies being inoculated into tubes of Medium A. These tubes should now contain the organism in pure culture, and further fermentation should proceed at a more rapid rate. In view, however, of the small amount of inoculum obtained from the scrapings two days may elapse before even slight fermentation is visible; but when once established the culture should be pasteurized and inoculated heavily into several tubes. Two or three tubes at least of an actively growing culture obtained as above should be then inoculated into a warm flask of the starch medium containing one litre of 6 per cent. mash. (Approximately 50 c.cm. of actively growing inoculum are required for one litre of mash.)

The flasks should be incubated until fermentation is completed, usually thirty-six to forty-eight hours being required in a good fermentation. The contents of the flask are then distilled and the distillate examined quantitatively for acetone and butyl alcohol, and qualitatively for diacetic and oxybutyric acids. The presence of a good fermentation is represented visibly by the evolution of a considerable amount of gas, which consists of CO₂ and H₂. This may be so vigorous that the plugs of the tubes or flasks, if caked with inspissated mash, may be blown out. Meanwhile, the starch is being split up by the diastatic ferment liberated by the growth of the bacillus, and a clear watery fluid forms in which masses of partially digested starch may be carried up to the surface, there to form a head in the tube or flask. This head later sinks and a clear supernatant watery fluid remains.

In the above method, if it is desired to dispense with the solid medium in the anaerobic tube, the only other method available is to take a number of tubes containing high dilutions of the bacteria and to attempt, by repeated pasteurization, incubation, and dilution, to obtain the organism in pure culture.

It cannot be too clearly indicated, however, that there are numerous impurities which will prevent the fermentation from being carried out, and the only way in which good fermentations can be obtained is apparently by the simultaneous growth in masses of large numbers of the organisms. Reference will be made to these impurities later in regard to treatment. It is probably only on account of the presence of other bacterial impurities in the food within the alimentary canal that diabetes is not a more rapidly fatal disease—these impurities lowering the yield of acetone bodies which would otherwise be formed. Further, the great difficulty of carrying through a fermentation *in vitro* from such highly infected material as faeces cannot be too clearly indicated.

Description of Organism.

The organism isolated is a Gram-positive rod-shaped bacillus and is a facultative spore-forming anaerobe. The bacillus is usually straight, 4 to 6 μ in length, and about 0.9 to 1.2 μ in thickness. The ends are slightly rounded. It may occur singly or in chains of two to six organisms, or the forms may lie parallel, two or three parallel forms being fairly common, and parallel forms may be present even when the members are existing in chain formation. It is possible that this may represent fission in two planes—longitudinal and transverse. Young cultures are slightly motile, and in forms more than twenty-four hours old central spores may develop. The spores are oval in shape, protrude beyond the width of the bacillus, do not take the Gram stain, and usually have a small vestige of bacillary protoplasm left at each end. This vestige tends ultimately to disappear in older spores. The bacilli take basic stains, being well stained by carbol fuchsin (1 in 10), and less definitely stained by methylene-blue. The Gram staining in young forms is quite definite. We suggest that the term *Bacillus amylobacter intestinalis* be applied to the organism as found in the intestine of man.

Result of Fermentations.

By the activity of the organisms proteolytic and diastatic enzymes are liberated. The diastatic enzyme, by its action, splits up starch; the proteolytic enzyme is manifest by the slight liquefaction of gelatin which occurs round the site of the colonies produced in Medium B. The organism develops best under anaerobic or partially anaerobic conditions, these conditions being satisfied when cultures are inoculated to the bottom of the tubes or flasks containing a well-gelatinized mash. In order to obtain an active fermentation of starch it appears necessary for a liberal amount of inoculum to be added (up to 5 per cent. of the tube or flask to be inoculated), since the fermentation appears to be retarded and even suppressed unless a large mass of organisms is growing simultaneously in one part of the medium. It is not, therefore, a good method to disseminate too freely the inoculum added.

The bacilli require a small quantity of protein with their starch, but experiments in hand appear to show that peptone can be substituted for protein, although it was at one time considered that peptone would not suffice. (See also *Journ. Biol. Chem.*, 1919, 39, 1-21.)

If the reaction of the mass is taken in which fermentation is actively proceeding it is found to rise rapidly, ultimately all on completion as follows:

1. Before incubation 10 c.cm. of mash required 0.3 c.cm. N/10 NaOH to neutralize.
2. After twenty-four hours 10 c.cm. of mash required 3.96 c.cm. N/10 NaOH to neutralize.
3. After forty-two hours 10 c.cm. of mash required 2 c.cm. N/10 NaOH to neutralize.

In addition there is a considerable evolution of gas, which is found to consist of hydrogen and CO₂. The estimation of the acidity can be regarded as indication of the progress of fermentation.

Examination of Products of Fermentation.

The signs of completed fermentation are cessation of gas evolution, and no further fall in the acidity of the liquor. The final acidity in a normal fermentation is such that 10 c.cm. of the mash require 1.8 to 2.5 c.cm. of N/10 NaOH for neutralization. (Boil off dissolved CO₂ before testing the acidity, and use phenolphthalein as an indicator.) The mixture of acetone and alcohols is referred to as mixed oil, and the estimation is carried out as follows:

The plug of the flask is removed and replaced by a stopper carrying a tube to a condenser, and the mash is distilled until no further oily drops are noticed in the condenser. Usually this distillate is 10 to 15 per cent. of the total volume in the first flask. The distillate is saturated with common salt and redistilled until no further oily drops are noticed.

The second distillate is saturated with anhydrous potassium carbonate and poured into a measuring cylinder. The potassium carbonate solution settles to the bottom, and there is a very definite dividing line between this and the layer of oil. The volume of mixed oil obtained is read off on the cylinder. (If preferred, it may be separated in a separating funnel and weighed in a closed bottle.)

For estimation of the acetone in the mixed oil, the latter must be diluted to a suitable strength. If 25 c.cm. of iodine are used in the iodoform estimation the amount taken should contain about 0.01 gram acetone. For example, if the mixed oil contains approximately one-third its weight of acetone, 10 c.cm. are taken and made up to 100 c.cm. Then 10 c.cm. of this dilution are taken and made up to 250 c.cm., and 10 c.cm. of this last dilution will contain approximately 0.01 gram of acetone, and it is the amount used for titration.

Take 10 c.cm. of this diluted liquor, add 25 c.cm. N/10 iodine solution and 6 c.cm. of 20 per cent. NaOH solution; allow to stand for five minutes, then add 6 c.cm. of 20 per cent. HCl and titrate the liberated iodine with sodium thiosulphate (N/10). This gives the amount of iodine not used in the making of iodoform from the acetone, so that the difference between 25 c.cm. and this figure is the amount of iodine used; 1 c.cm. of N/10 iodine is equivalent to 0.000967 gram acetone.

Results of Case Examination.

The results obtained in cases in which fermentation was carried to completion were as follows:

Urine Examination.

Patient.	Sugar (Grams per Litre).	Diacetic Acid.	Acetone (Grams per Litre).
Ma. ...	45.4 grams	Present	0.72 gram.
Ho. ...	40.5 "	Present	0.047 "
Wa. ...	20.0 "	Large amount	0.037 "
Ba. ...	42.7 "	Present	0.70 "
Br. ...	30.0 "	Present	0.25 "

Stool Examination.

Patient.	Acetone in Stool as Percentage on Dry Stool.	General Remarks as to Bacteriology, etc.
Ma.	0.06 per cent.	B. amyloclasticus intestinalis present; also a long, thick bacillus from which it had to be freed by repeated pasteurization and sub-culturing.
Ho.	0.043 per cent. with in addition acetone bodies equivalent to 0.02 per cent. crotonic acid	B. amyloclasticus intestinalis found.
Wa.	Not examined	B. amyloclasticus intestinalis found.
Ba.	0.036 per cent.	B. amyloclasticus intestinalis.
Br.	0.08 per cent.	B. amyloclasticus intestinalis.

Fermentation on Starch Media by Organism Isolated from Stool in each Case.

Final acidity of mash being approximately 2 c.cm. N/10 NaOH to neutralize 10 c.cm. in each case.

Patient.	Mixed Oil Products.	Percentage Weight of Acetone on Starch.	Nature of Oils.
Ma.	20 c.cm. on 55 gm. starch and 5 gm. oatmeal	9.2	N butyl alcohol equivalent to twice amount of acetone present.
Ho.	17.2 c.cm. on 54 gm. starch and 6 gm. oatmeal	6.8	Diacetic acid and N butyl alcohol present. Trace of iso-butyl alcohol.
Wa.	9 c.cm. on 25 gm. starch and oatmeal	6.6	Acetone and N butyl alcohol.
Ba.	13 c.cm. on 50 gm. rice and 5 gm. oatmeal	5.8	N butyl alcohol and acetone.
Br.	10 c.cm. on 27 gm. rice and 3 gm. oatmeal	5.2	Acetone; N butyl alcohol; trace iso-butyl alcohol.

The alcohols were identified by preparing the 3.5 dinitro-benzoyl esters and examination of the same.

Altogether nine cases of alleged diabetes have been under examination. Of these, five have been completed, and the results are indicated in the tables. The remaining four are receiving further experimental work. The organism has been detected microscopically in two of the remaining cases, but with it foreign organisms, which have retarded its action in the complete massive fermentation of starch, and great difficulties have been met with in obtaining the organism in pure culture.* There is sufficient indication that in a short time these difficulties will be overcome and that the experimental results can be added to the five reported cases. Of the other two, one shows glycosuria following emotional disturbances, and the other is a young child now rendered sugar-free. As controls, eleven non-diabetic stools have been examined, and the organism has not been detected in any case.

Occurrence of Similar Organisms in Nature.

The acetone bacillus which was used during the war was believed to occur on decaying maize, on bad potatoes, and on other decaying vegetable matter. Northup isolated *B. aceto-ethylicum* from bad potatoes. Jute retting is supposed to be due to a similar organism, and in this respect the incidence of diabetes in Dundee amongst jute workers is highly suggestive of a bacterial infection by our bacillus. Occurring as it does on decaying vegetable life it is easy to understand how such a heat-resistant, spore-forming organism should enter the alimentary canal of human beings. It is probable that, if this be so, one of the post-war effects will be a considerable increase in the incidence of diabetes and of acidosis.

Discussion of Results with a View to Treatment.

The degradation of the complex starch molecule probably occurs by the formation of fatty acids with large molecules and then successive oxidation of two carbon atoms at a time, starting in the beta carbon atom. Ultimately, through the stage of intermediate fatty acids, the four-carbon fatty acid (butyric acid) will be arrived at. Oxidation will proceed normally at the beta carbon atom, producing the beta oxybutyric acid; this is capable of further oxidation at the same point to aceto-acetic acid, and this will be ultimately broken up, giving acetone and CO₂. The changes can be followed by means of the following formulae:

* Since this article was prepared for press one of these two has given typical fermentations.

Thus it would appear that the beta oxybutyric acid and the aceto-acetic acid produced in the course of the disease are intermediate products leading ultimately to acetone, providing the conditions are favourable. This conclusion is supported by the observations on the fermentation, where it is noted that the end of the reaction is determined by the fall in the acidity of the mash.

The fact that the alcohols produced in the fermentation are not detected in the excreta of diabetic patients can be explained to some extent by their absorption and possible oxidation in the liver to products which would not be easily detected. Stepp⁷ claims that he has detected aldehydes (or substances which react in every way like aldehydes) in the blood of diabetic patients. Aldehydes would be the first products of the oxidation of normal alcohols, and complete oxidation would lead to CO₂ and water. In endeavouring to obtain good yields of acetone the inhibitory effects of certain bacteria came to be recognized. Thus Thaysen states that the organism which causes most damage to a fermentation is the *B. volutans*. Others have described the *B. acidi lactici*, and we have found the presence of a diplococcus and of a large thick bacillus, of unknown identity as yet, to be responsible for much inhibition. It appears probable that these facts, combined with a diet so composed as to allow digestion and absorption by the patient of foods which the bacteria cannot assimilate, will prove an important part of treatment, combined with the administration of certain antiseptics. In this respect the authors⁸ would call attention to their work on the subject of antiseptic action amongst the coal-tar dyestuffs, which gives useful data as to the relative value of dyes as antiseptics in regard to different organisms.

SUMMARY.

1. From the stools of diabetics a new organism (*B. amyloclasticus intestinalis*) has been isolated which splits up starchy foods, forming oxybutyric acid, diacetic acid, butyl alcohol, and acetone. Sugar is also formed during this fermentation.

2. Acetone has been found in quantities capable of estimation in the stools of diabetics.

3. In diabetes carbohydrate fermentation occurs in the alimentary canal, forming abnormal products which probably so affect the glycogenic function of the liver as to lead to improper storage therein of the glucose from the alimentary canal during digestion.

4. Definite lines of treatment include elimination or suppression of this organism.

We wish to express our indebtedness for access to diabetic cases to Dr. J. Gray Clegg, Dr. Wm. Stirling, and Dr. Langley; and to Mr. A. Gill, B.Sc., for his technical assistance with the various processes herein detailed.

REFERENCES.

- ¹ Schirdinger: *Centralbl. f. Bakteriolog.*, 1905, 14, Abt. ii, 772. ² Brede-mann: *Centralbl. f. Bakteriolog.*, 1909, 23, Abt. ii. ³ Fernbach and Strange (Eng. Pat. 1912, No. 21,073). ⁴ Northup, Ashe, and Senior: *Journ. Biol. Chem.*, 1919, 39, 1-28; *Journ. Ind. Eng. Chem.*, 1919, 11, 723-27. ⁵ Amos Gill: *Journ. of Society of Chemical Industry*, July 31st, 1919, vol. xxxviii, pp. 273-80. ⁶ Thaysen: *Journ. of Institute of Brewing*, vol. xvii, No. 11, pp. 529-542. ⁷ Stepp: *Biochem. Zeit.*, 107, 60-80 (1920). ⁸ Fairbrother and Renshaw: *Journ. of Path. and Bact.*, vol. xxv, 1922, pp. 145-151.

FRAGILITAS OSSIIUM ASSOCIATED WITH BLUE SCLEROTICS IN FOUR GENERATIONS.

BY

J. BROWNING ALEXANDER, M.D., M.R.C.P.LOND.,
PHYSICIAN WITH CHARGE OF OUT-PATIENTS, PRINCE OF WALES'S
GENERAL HOSPITAL, AND CITY OF LONDON HOSPITAL
FOR DISEASES OF THE CHEST.

INSTANCES of fragilitas ossium associated with blue sclerotics have from time to time appeared in medical literature, and as recently as December 24th, 1921, Blegvad and Haxthausen of Copenhagen reported in the BRITISH MEDICAL JOURNAL cases showing, not only blue sclerotics and brittle bones, but also associated with macular atrophy of the skin and zonular cataract. Such cases are, however, sufficiently rare to warrant putting on record the following history:

The patient, F. F., aged 7½ years, presented himself at my out-patient department about a year ago. The history was that he suffered from repeated fractures—the most recent having been one of the lower end of the right tibia. Some deformity was present in the right leg and the right thigh, and it was ascertained that both the tibia and the femur had been previously fractured—the latter having occurred at birth. In addition a history was obtained of past fractures of the left humerus and the tibia and fibula of the left leg. These had healed with apparent perfect union and minimal

amount of callus. The most striking feature which one observed when the boy entered the consulting room was the marked blueness of both sclerotics. The child was somewhat pale and debilitated, the forehead more prominent than normal, but no evidence of rickets was apparent. In other respects the mother stated that the boy had always been healthy. The mother, to whom the boy bore a strong resemblance, showed very deep blue sclerotics. She had, however, no fractures. Her hearing was defective, and she informed me that she had suffered from deafness for many years. The patient's two sisters, whom I saw later, also presented blue sclerotics, with, however, no history of fractures. On inquiring further into the history of the family I found that the aunt of the patient (the patient's mother's sister) had sustained altogether seven fractures during her life and had, as in the other members of the family, deep blue sclerotics. The grandmother and great-grandmother had both been the subjects of fragile bones and blue sclerotics. No further history of these phenomena was forthcoming in previous generations to the ones already mentioned; it is quite possible, however, that a careful study of this family's genealogy would have revealed the same condition in former generations.

This remarkable association of brittle bones and blue sclerotics was first described by Eddowes in 1900, who suggested that "the transparency of the sclerotics indicated a want of quantity or quality of fibrous tissue forming the framework of the various organs of the body, and probably explained the want of spring or toughness in the bones of these individuals." The importance of heredity in these cases was most clearly indicated by Stephenson and Harman in 1910, who published accounts of the same family of blue sclerotics—altogether 55 individuals in five generations, 31 of whom showed typical sclerotics. No mention was then made of fragile bones; but in 1915 Stephenson showed at the London Ophthalmological Society a mother and two daughters with fractures, belonging to this family. Rolleston, in 1911, reported 4 cases of blue sclerotics in three generations, with fragile bones occurring only in the third generation. Peters, in 1908, published the account of blue sclerotics in a family during three generations, and five years later further reported the occurrence of fractures in these cases. The interesting case reported by Ostheimer in the *Journal of the American Medical Association* of December, 1914, had blue sclerotics and nine fractures between the ages of 1½ and 4 years. In this case there was no history of the condition occurring in other members of the family. The literature of the subject is further enhanced by the publication of similar cases by Burrows, in 1911 (a family of 29 individuals—13 with blue sclerotics, and 9 of the 13 with brittle bones); Poynton, in 1913 (1 case); Hoffmann, in 1915 (3 cases); E. Bronson, in 1917 (description of two families); and Olaf Blegvad and Holger Haxthausen, *BRITISH MEDICAL JOURNAL*, December 24th, 1921.

There seems to be little doubt that the blueness of the sclerotics is due to the increased transmission of the colour of the choroidal pigment and not to any inherent colouring of the sclerotics themselves. Some think, however, that there is an actual thinning of the sclerotics. Fridenberg has suggested that the blue sclerotics are due to a transparency depending upon the absence of lime salts in the connective tissue of the sclera. The long-standing deafness in the case of the mother described is worthy of notice, and might possibly be explained, as Bronson suggested, by a deposition of calcium salts in the middle ear, relating to the abnormal osteogenetic process.

THE RECOGNITION AND TREATMENT OF MINOR DEGREES OF FIBROSITIS.

BY

THOMAS MARLIN, M.D., D.P.H., D.M.R.E.,
ASSISTANT ELECTRO- AND PHYSIO-THERAPEUTIST TO THE MIDDLESEX
HOSPITAL.

KNOWING the danger of missing an internal lesion which may be associated with superficial pain we naturally in such cases look for some objective sign. Failure to realize that the cause of many pains can be definitely detected in the soft tissues may explain why their examination is neglected. A patient who complains of pain in the region of the right scapula may be taken as an example. There may be some tenderness on pressure over a particular area, but otherwise nothing definite is noted; there is no swelling, no grating in the joints, and the lungs and heart are normal. The teeth may be surveyed and search made for some source of infection or irritation, without finding anything to confirm the patient's statement. If, however, we now devote a little