ended at or near the perineum, an anal depression was present in all; in 10 cases where the rectum ended blindly at or above the vagina, the proctodaeum was well developed in 7, partly developed in 1, and absent in 2. Amongst males with the rectum opening into the urethra there were 7 with the proctodaeum well marked, 3 with it partly developed, and an uncertain number in which it was absent. In 7 males in which the rectum terminated blindly at or above the prostate the proctodaeum was present in 4, absent in 3; where the rectum nearly reached the perineum the proctodaeum was well marked in all cases, partly developed in 2, and absent in 1.

In 2 cases, both females, the epithelium of the proctodaeum had budded out irregularly, so as to form diverticula, some of which projected for some distance into the perineal tissue, and undoubtedly correspond to certain diverticula which are found in the anal canal opening under the folds which join together the upper ends of the columns of Morgagni, and which were first pointed out to me by Mr. J. Bernard Dawson.

Associated Malformations.—The following is a list of the lesions associated with imperfect rectum in the human specimens examined for the purposes of this demonstration:

Retained testis	...	...	...	1
Malformed coccyx	...	...	...	2
Imperforate urethra	...	...	...	2
Dilated bladder	...	...	...	5
Low implantation of ureter	...	...	...	3
Occlusion of ureter	...	...	...	1
Urachal fistula	...	...	...	1
Hypospadias	...	...	...	1
Ectopia vesicae	...	...	...	1
Talipes	...	...	...	1
Cord to coccyx	...	...	...	1
Right arm deformed	...	...	...	1
Compressed pelvis	...	...	...	2

RESULTS OF OPERATION.

I do not propose to deal with the operative procedures to be adopted for the treatment of malformation of the rectum, but a study of these specimens has forced several matters on my attention. One is the great danger of using a trocar for the relief of the condition; there are eleven preparations mounted purposely to show perforations into the pouch of Douglas or a separation of the coats of the rectum by the use of the trocar; Curling and Harrison Cripps have emphasized the danger of the trocar. There should be no half measures in operating; in 95 per cent. of cases it is physically possible to bring the rectum down to the perineum; if it be not found terminating at the site of the proctodaeum, it will be found perforating the prostate or the lower end of the vagina; if not there, then at the base of the prostate or upper part of the vagina. If unrelieved, death occurs about the fifth day from gangrene and rupture, usually towards the upper part of the colon. The prognosis is bad; an imperforate condition of the rectum appears to react on the economy of the child even before birth, and death commonly ensues, even if the rectum be opened early. The prognosis is favourable in the case of females where the rectum opens in the vulva; in all cases hypertrophy and dilatation of the rectum follows, even if an anus is successfully established. It is important to remember that the external sphincter and also internal sphincter are developed in connexion with the perineum, not with the bowel; hence, if a proctodaeum be present, the surgeon may rely on obtaining an orifice provided with competent sphincters.

[Besides the authorities cited below, the following works may be consulted with advantage: Ballantyne's *Antenatal Pathology*; Dr. William Wright's Report on Recent Teratological Literature, published annually in the *Journal of Anatomy and Physiology*; *The Rectum and Anus*, by Sir Charles Ball.]

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FOOD EXTRACTS MADE FROM YEAST.

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In a recent communication¹ dealing with the relative properties of food extracts made from meat on the one hand, and from yeast on the other, Professor Gamgee discusses the subject in a manner which seems to call for some reply, if only on the principle that it is always well to "hear the other side." In this article I propose to deal entirely with the scientific aspects of the question, and not to touch upon commercial issues.

As one who has been familiar with the chemistry of meat extracts for many years, and who has devoted a considerable amount of practical attention to the chemistry and technology of yeast extract, even before it was manufactured to any extent in this country, I may perhaps venture to claim in this short article the attention of those of your readers who are interested in the subject.

Professor Gamgee's communication can be divided, broadly speaking, into two parts, the one dealing with a comparison of the chemical constituents of extract of meat and extract of yeast, and the other being an attempt to show that the former is beneficial and the latter prejudicial to the human—especially the gouty—organism. Both extract of meat and extract of yeast are, as is well known, highly-complicated mixtures, containing a very large number of nitrogenous and non-nitrogenous substances, of which only some have been isolated or identified. From time to time the presence of new bases and other constituents in both forms of extract is recorded, and it has to be admitted that our knowledge of the chemistry of both these products is exceedingly imperfect. As an instance, I may refer to some papers recently published by Kutscher,² who has obtained from meat extract several hitherto unknown bases to which he gives the names ignotine (?identical with carnosine), novaine, carnitine, oblitine, vitatine, etc., and it is more than probable that others still remain to be discovered in both yeast and meat extracts.

The important bearing of this consideration on the subject under discussion will be obvious a little later. It will not, I think, serve any useful purpose to give a list of all the substances which are known to exist in meat and yeast extracts, the more so as such a list must necessarily be very incomplete, and I propose to deal in the first place with the main compositional resemblances, and then to refer to those differences which exist, or are alleged to exist.

Extract of meat, consisting as it does of a concentrated aqueous infusion of meat, contains those soluble substances which are present in the muscular tissue of the ox, or occasionally of some other animal. These may be roughly classed as nitrogen-containing bodies, non-nitrogenous extractive matters and inorganic salts. Extract of yeast, which is prepared by the suitable treatment of yeast plasma, consists of substances which may be classed in the same three categories. Assuming the same degree of concentration—that is, equal percentages of water in both forms of extract—then the proportions in which these three main groups of constituents exist are practically the same. Taking first the mineral matter: this consists in both cases largely of alkaline chlorides and potassium phosphate. The non-nitrogenous extractive matters consist in both cases of glycogen with other carbohydrates, such as gums, inulin, etc., and lactic acid. Much work remains to be done in connexion with this part of the subject; but as the non-nitrogenous constituents are not usually credited with much physiological activity, it will not be necessary to say more than that the carbohydrate extractives of meat extracts have their counterparts in the extract prepared from yeast.

We now come to the important nitrogen-containing substances to some of which the physiological effects of both classes of extracts are due. It is with these substances that Professor Gamgee almost exclusively concerns himself, holding quite rightly that meat extracts (and the same is equally true of yeast extracts) are not foods in the true sense of the word, but rather food adjuncts or stimulants, and that certain of the nitrogenous bases are the only bodies present in these extracts which are known to be possessed of marked physiological activity.

Proteoses, peptones, and other of the higher products of the hydrolysis of complex albuminoids are sometimes present in both meat and yeast extract, their presence and proportions depending largely on the manufacturing conditions adopted, but they are more often absent or present in such small proportions that they may, for the purpose of this paper, be disregarded. Leucine and tyrosine, two splitting products of the proteins, are present in both extracts. The other nitrogen-containing bodies are creatine and creatinine and the so-called purin bases.

As I am dealing in the first place with compositional resemblances, I will discuss the purin bases first and refer to the question of creatine and creatinine afterwards.

Uric acid and a number of allied substances which are formed by the breaking down of proteins have been shown by Emil Fischer to be constitutionally and genetically related to a crystalline substance (not "a hypothetical body, $C_5H_4N_4$ ") obtained by him in 1897, to which he gave the name *purin*, and which has the formula $C_5H_4N_4$. Such substances are hypoxanthine, xanthine, guanine, adenine, theobromine, and caffeine, and it is these to which the designation of "purin bases" is applied. In the present connexion we need concern ourselves only with the first four, which are present in both meat and yeast extracts. Some doubt exists; it is true, as to the presence of guanine in meat extract; but as this base has not been observed to possess any toxic or other marked physiological activity, the question is of but little more than academic interest. It is probable, however, that it occurs in all meat extracts in small but varying proportions, depending on the extent to which the des-aminating enzyme is allowed to exert its activity. We now come to the statement to which Professor Gamgee gives especial prominence—namely, that whilst hypoxanthine is the predominating purin base in meat extracts, in yeast extract it is adenine. I propose to examine, in the first place, the evidence on which this statement rests; and, in the second, the justification for the very definite and important conclusion which Professor Gamgee has drawn from it. Kossel was, I believe, the first to state that adenine and guanine occurred in larger proportions in yeast than in meat extracts; and more recently H. Micko,³ to whom we are indebted for much valuable work on the analytical chemistry of the purin bases, has examined side by side a sample of Liebig's extract and one of yeast extract and arrives at the same conclusion. It must not, however, be overlooked in this connexion, that there are great differences in the composition of commercial extracts of yeast, just as there are in the various meat extracts; differences which are dependent not only on the character of the yeast employed, but to a far greater extent on the method adopted in the manufacture of the extract. The method of preparation described by Professor Gamgee is very incomplete, and reads like an abstract of a patent specification rather than a description of a complicated and delicate technical process, in which the character and quality of the finished product are very largely dependent on the observance of conditions which are not even alluded to in the statement in question. The importance of such working conditions will be manifest when it is remembered that the yeast cell is the home of a number of enzymes on the activity of which the composition of the finished extract so much depends.

It has been shown by many workers⁴ that many organs of the body contain des-aminating enzymes—that is, enzymes capable of converting the amino-purins, such as adenine and guanine, into the corresponding oxy-purins, such as xanthine and hypoxanthine. This doubtless explains the preponderance of the oxy-purins in meat extract, and there is no evidence that a similar action does not come into play under suitable conditions in the case of extract of yeast. In any case, Professor Gamgee appears to rely solely on the results of an examination by Micko of one sample of yeast extract—namely, "Dresdener Würst- und Brau-Extract," which is very dissimilar from the British extract "marmite," which is singled out by him for special criticism. As showing the extent to which these extracts vary, I may point out that I have on two occasions carried out on large quantities of "marmite" extract experimental investigations similar in character and method to those made by Micko, and I have found that the base hypoxanthine was present in greater amount than either guanine or adenine. I may add that I worked in each experiment on 1 kilogram of the extract

and separated and isolated the bases. There is, therefore, no foundation for the unqualified assertion that yeast extracts contain much larger quantities of adenine than of hypoxanthine. Some may, others certainly do not. It is, however, probable that all yeast extracts do contain more adenine than meat extracts of the same degree of concentration, and it may be of interest to quote the paragraph in which Professor Gamgee refers specifically to the physiological effects of this base. He says:

Although these bodies [hypoxanthine and adenine] are closely related, and all the purin bases, in greater or less proportion, are generators of uric acid in the animal organism, our knowledge in no respect permits us to affirm that the adenine of yeast extract is not a much more injurious body in so far as the animal body is concerned than the hypoxanthine of beef. [The italics are mine.]

The precise wording of this statement is worthy of note, since read with its context it seems to cast a slur on the reputation of adenine in the absence of any facts which would have justified a definite charge.

It is a little unfortunate for Professor Gamgee's argument that whilst adenine passes almost unchanged through the organism, more than one-half of any ingested hypoxanthine is excreted in the urine in the form of uric acid. This is clearly shown by the experiments of Burian and Schur, Walker Hall, Hopkins, Minkowski, and others. Kaufman and Mohr⁵ have, moreover, shown that from 48 per cent. to 85 per cent. of the hypoxanthine in beef is excreted as uric acid. Professor Gamgee further states in support of his case against yeast extracts that these contain larger quantities of purin nitrogen than meat extracts, presumably of similar water contents. My own analyses show that this is not by any means the case, considerable variations occurring in both forms of extract. Thus, working by Micko's method, I have during the last few weeks found 0.81 per cent. of purin nitrogen in a sample of Lemco, and 0.83 per cent. in a sample of ordinary pot marmite of similar concentration. Micko himself⁶ recorded 0.648 per cent. as the mean of four estimations in Liebig's extract and 0.509 per cent. in a sample of yeast extract known as "Bios." Graff⁷ records 0.795 per cent. and 0.687 per cent. purin nitrogen respectively in two well-known brands of meat extract. For purposes of argument, however, I will assume that Professor Gamgee is correct, and that meat extract contains an average of 0.43 per cent., and yeast extract an average of 0.64 per cent. of nitrogen existing as purin bases, although there is no doubt that these numbers are wholly incorrect. I will in addition make the reasonable assumption that this consists chiefly of hypoxanthine, and that the factor 2.43 must consequently be used to convert nitrogen into the base. The difference between the yeast and meat purin nitrogen would be $0.64 - 0.43 = 0.21$ per cent., which multiplied by 2.43 = 0.51 per cent. of purin bases. That is to say, a person eating 1 oz. per day of yeast extract would actually ingest in twenty-four hours 2.23 grains more of purin bases than if he had consumed the same quantity of extract of meat! Surely Professor Gamgee will not contend that such a quantity is sufficient to produce any disturbance even in a gouty organism, or that it is of a nature to justify any responsible person in attacking a properly-conducted industry. I have only dealt at some length with the bases hypoxanthine and adenine because Professor Gamgee has laid such stress upon them, but to what extent these substances are responsible for the therapeutic properties of meat and yeast extracts is at the present moment quite unknown.

Slade⁸ has recently devoted some attention to this point, and in this connexion it may be well to quote from Professor Halliburton's 1907 report to the Chemical Society on recent progress in physiological chemistry. Under the heading, Other Bases in Meat Extracts, he says (page 239):

Kutscher has been diligently exploring this neglected corner of the physiological field, and has discovered a number of new bases in addition to others which, like creatine, creatinine, choline and neurine, were known previously. The new bases are labelled with quaint names, such as ignotine, novaine, carnitine, vitiatine, etc., a fact which in itself reveals how scanty is the present knowledge of their chemical composition. The good effects of beef-tea as a stimulant in disease are well known; its harmful action, however, is not yet so widely recognized by the medical profession, and yet this is very marked in certain pathological conditions; no doubt some of the bases

alluded to are the toxic agents. A preliminary investigation with a view to determining this more accurately has been published by Slade, but the deductions as to which constituents the powerful action of meat extracts is due are put forward with reserve. In moderate doses the heart's rate and force are increased; this is not due to creatine, xanthine, or urates; the increase in the movements of plain muscle all over the body is probably produced by ornithine and novaine; the agents concerned in causing diuresis, purgation, and other symptoms are quite unknown.

In a word, we are quite unable to reason from the (imperfectly) known composition of extracts of meat and of yeast as to their probable physiological effects, and in both cases the proof of the pudding is entirely in the eating. In making this statement I am supported by the authority of an eminent physiological chemist, who has made a special study of purin metabolism and the uric acid question.

That being so, I would point to the fact that for a number of years yeast extract has been consumed, in many cases regularly, by thousands of persons in quantities amounting in the aggregate to many hundreds of tons, and it is only reasonable to suppose that some of these were the "gouty and arthritic amongst us," who would surely have communicated with their medical attendants had the consequences been, even in a slight degree, such as are implied in Professor Gamgee's article. As a matter of fact, feeding experiments with healthy persons and with invalids have been carried out by Dr. Lebbin, for many years chemist to the Ministry of War, and to the Chief of the Royal Police, Berlin, and by Dr. Goliner, both of whom report that their results show that in all cases the yeast extract compared favourably in every respect with meat extract, both as a stimulant and a savoury food adjunct. On page 452 Professor Gamgee refers to Pawlow's well-known experiments on the stimulation of the gastric secretions, and makes the statement that yeast extracts "contain none of the flavouring and odoriferous principles which cause extract of beef to be palatable." I can only suppose that Professor Gamgee has never had in his hands a well-made sample of extract of yeast, or he could scarcely have given utterance to such a statement. Even the earlier Continental preparations were so similar to extract of meat that Lafar in his *Technical Mycology*, vol. ii, p. 168, says

and as a matter of fact some of the preparations of this kind (that is, yeast extracts) already sold are indistinguishable by the laity from real meat extract, so far as the smell, flavour, and external appearance are concerned.

The aromatic principles and those which provoke the secretion of gastric juice are present in yeast extract as in meat extract, but the aroma is in the best preparations more pleasant and free from the suggestion of putrefaction, which is sometimes noticeable in inferior extracts of meat. It is in fact noteworthy that certain bacteria which are responsible for putrefactive change develop much more easily in extract of meat infusions than in those prepared from extract of yeast.

Having devoted attention to those many points in which the two kinds of extract resemble one another closely, I now come to the only marked chemical difference with which I am acquainted—namely, the presence of creatine and creatinine in the extracts of meat and its practical absence in those made from yeast. It may be well here to correct a misapprehension under which Professor Gamgee appears to labour. The colorimetric method of Jaffé does not depend on the formation of creatinine picrate, but on the fact that the creatinine, which is a powerful reducing agent, reduces the picric acid in alkaline solution to picramic acid and diamido-nitro phenol, the alkaline salts of which are deeply coloured, and so may serve under closely-defined conditions for the colorimetric estimation of creatinine, or indirectly of creatine. I do not propose to deal more fully with this question here, as I am shortly publishing a communication on the subject elsewhere. In regard to the very high results for the creatine and creatinine percentages in meat extract to which reference is made, Professor Gamgee does not appear to be aware that Emmett and Grindley have quite recently⁹ published a paper dealing exhaustively with the Jaffé method, and indicating the limiting conditions necessary for obtaining accurate results. They have, moreover, confirmed their earlier numbers for the percentages of creatine and creatinine in meat extracts—namely, up to 6.5 per cent.—the numbers being of the

same order as those obtained by Bauer and Barschall, by Grindley and Woods, and others. Professor Gamgee further remarks, on page 449, that the amount of creatine plus creatinine in extracts of meat is remarkably constant. It is interesting in this connexion to note that analyses of Lemco recently made in the *Lancet* laboratory and published in the October 24th, 1908, issue of that journal, p. 1241, show numbers varying from 9 per cent. to 14.28 per cent. for the combined bases in samples of Lemco of approximately the same moisture content (17.5 per cent. to 20.2 per cent.). This point is, however, of very little importance from the point of view of Professor Gamgee's main argument, the only question being whether these two bases are valuable constituents of extract of meat. Here it may be said at once that all physiological chemists who have studied the subject are agreed that these substances are not known to possess any physiological significance. Professor Gamgee suggests that they may be useful, but that is scarcely a form of argument which calls for serious notice. Some few years ago Dr. J. W. Mallet carried out for the United States Government an extensive and detailed investigation "On the Physiological Effect of Creatine and Creatinine and their Value as Nutrients," and his report was issued as a *Bulletin* of the United States Department of Agriculture. After pointing out that very large doses (2 grams) of these bases produced no appreciable physiological effect, and that, beyond the retardation of the action of the heart, doses of 5 or 10 grams did not give rise in the human subject to any serious effects, he goes on to say:

Even if viewed in the light of nerve stimulants only, and thus to be classed with tea and coffee as adjuncts to food rather than as true food itself, meat extracts so far as the flesh bases creatine and creatinine are concerned are shown by this investigation to be very much less active in their effects upon the nervous system than they have been commonly reputed. The potassium salts present in large quantity in meat extracts are by no means to be overlooked as influencing such effects as are produced upon the living organism, and it may be that some of the minor organic constituents are relatively more potent than creatine and creatinine, but aside from such real proteid or peptonic material as is in some cases present, the meat extract preparations may fairly be relegated on the whole to the class of condiments or flavouring matters rather than to that of foods or medicines.

I believe I am right in saying that this view either in its entirety or with slight modifications is very generally accepted by all who are qualified to form a judgement.

In conclusion I will take the summary of Professor Gamgee's points in the order in which he states them in Section IV of his paper.

1. "Yeast extract differs from meat extract in a startling manner." Apart from the presence of creatine and creatinine in the latter, and its absence in the former, there is no established difference of any importance. The creatine and creatinine are not known to possess any physiological value.

2. "They contain none of the flavouring and odoriferous principles which cause extracts of beef to be palatable." This is quite incorrect. In the case of the best preparations they are almost indistinguishable.

3. "They (yeast extracts) abound in the nucleo-proteids." This is not the case. The nucleo-proteids are destroyed in the process of manufacture.

4. "That the purin nitrogen contained in the yeast extract is half as much more as in meat extract." This I have shown to be a mistake, but, even if the statement were true, the fact would not, I maintain, have any practical significance with quantities such as are in question.

5. "That our knowledge in no way permits us to affirm that the adenine of yeast extract is not a much more injurious body, in so far as the animal body is concerned, than the hypoxanthin of beef." I contend that our knowledge in no respect permits us to affirm anything at all, as regards the relative injuriousness of these two bases, when dealing with such quantities.

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