and in one case neurological symptoms became apparent for the first time during treatment. Similar results are reported by Ungley.

(c) *Haematological*.—A tendency for the colour index to rise under marmite therapy, due to the increase of haemoglobin in relation to red cells, is seen in cases reported by Goodall, Ungley, and myself. No satisfactory explanation for this is available. As previously noted, yeast products are valueless in the treatment of iron-deficiency anaemias in human beings.

CONCLUSIONS

The therapeutic effects of yeast products in different types of anaemia are reviewed. Records of sixteen cases of Addisonian pernicious anaemia treated with autolysed yeast products or alcoholic extracts made therefrom are described and compared with the results of other workers in this field. The conclusion is reached that such products contain some haemopoietic principle, the value of which is discussed, but its concentration is small, as judged by many therapeutic failures, relative or absolute. For this reason, autolysed yeast products in their present form should not be used as substitutes for liver, liver extract, or hog's stomach tissue in the treatment of pernicious anaemia.

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SOME NEW OBSERVATIONS ON THE DIAGNOSIS AND TREATMENT OF SYPHILIS*

BY

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Contrary to the general impression, primary syphilis can cause symptoms before it has reached the stage when secondary signs are apparent. Anaemia, pains in the joints, persistent headache, nausea, and pyrexia occur in about 50 per cent. of primary cases, and in women these indications may justify the insertion of a vaginal speculum, which is essential if a chancre on the cervix is not to be overlooked.

It is commonly held that a primary lesion of the genitalia is always accompanied by a satellite bubo, but the absence of an inguinal lymphadenitis does not enable us to dismiss the possibility of syphilis. Internal chancres

drain into the common iliac and meso-rectal lymphatics, and even an external inoculation will cause enlargement of the inguinal glands only in about 40 per cent. of cases. To dismiss a sore on the external genitalia as being non-syphilitic because it is unaccompanied by an inguinal adenitis is therefore to incur error in a possible 60 per cent. of cases. To prevent these mistakes and to secure an accurate diagnosis at the earliest moment the dark-ground microscope must be used. Incidentally, many textbooks state that the enlarged glands which occur with a syphilitic chancre are small, hard, and shotty. On the contrary, they are generally large and elastic, and have a distinctive "indiarubbery" feeling which is characteristic of syphilis.

It is generally thought that the favourite site of inoculation is on the labia, but only 39.39 per cent. occur there, while in at least 44 per cent. of cases the primary lesion is on the cervix.¹ Owing to position, the majority of cervical chancres are undiscovered, or only diagnosed when the patient has developed secondary signs and symptoms. If the incidence of syphilis is to be reduced a larger number of these cases must be diagnosed during the first stage, so that the patient can be warned against infecting her consort. *The cervical chancre, hidden and painless, is the greatest cause of the spread of syphilis. It is the commonest source of infection because its presence is unsuspected by both sexes.*

In a series of 584 cases given by the author¹ the sites of primary genital chancres in women were distributed as follows:

	Number	Percentage
Cervix	257	44.00
Labia majora	183	31.33
Labia minora	47	8.06
Fourchette	33	5.65
Urethra	19	3.26
Clitoris	16	2.74
Vagina	8	1.37
Vestibule	6	1.03
Anus	5	0.86
Bartholin's orifice	4	0.68
Perineum	2	0.34
Thigh	2	0.34
Mons veneris	1	0.17
Buttock	1	0.17

Just as the varying gonococcal cervical discharge cannot be diagnosed by its clinical appearance so may cervical chancres range from an extensive carcinomatous-like ulceration to a small shallow abrasion. Irrespective of appearance, these clinical pictures are all deadly in their infectivity. However, certain characteristics of a cervical lesion—especially the edge and the colour—should rouse suspicion and urge us to "dark-ground" its serum. The edge of a cervical chancre, even when it is implanted on a pre-existing erosion, is generally well defined and regular. If the outline is carefully examined with magnifying spectacles, the defined regularity of the chancre's margin can be readily distinguished from the irregular raggedness of a non-syphilitic erosion. The colour of the erosive chancre, which is the common type of cervical chancre (about 71 per cent.),¹ is bluish-red, and is covered with small haemorrhagic spots, or, if it is not too recent, it may be covered with a thin greyish membrane, which also has a bluish tinge. The ulcerative type, which occurs in 24 per cent. of cervical chancres,¹ may be covered with a yellowish-grey slough, which only lasts for four or five days, and after that its base is covered by bluish-grey granulations which ooze blood and serum when touched. Although cervical chancres bleed easily those on the vulva do not. The bluish tinge of most cervical chancres is similar to the bluish colour of the congested vulva or cervix of a pregnant woman, but it is confined to the area of the chancre instead of affecting the whole cervix. This purplish or bluish hue, caused by the syphilitic infiltration of lymphatics and blood stasis, is a particularly

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useful diagnostic point in differentiating the common erosive chancre from the most numerous of lesions on the cervix—the simple erosions.

How does the gonococcal erosion differ from the chancre? The most frequent gonorrhoeal erosion—the papillary type—has a bright brick-red colour, with haemorrhagic points on its surface, which cause it to bleed more readily than a chancre. The outline may be ill defined and fade away gradually into the surrounding normal epithelium or it may be sharply circumscribed. When carefully examined, however, the margin is always irregular. The surface is velvety and smooth, neither elevated nor depressed; it is soft, and its limits cannot be felt. The discharge, which may be green, yellow, white, or clear and transparent, is abundant. The secretion from a chancre is scanty and serous. The differential diagnosis between the two conditions may be easy or difficult. If the usual characteristics of the chancre are present there is no confusion; but a small erosive type of chancre may be clinically indistinguishable from a small gonorrhoeal erosion.

Tradition and many textbooks inform us that hardness or induration circumscribed in the base of a sore means syphilis and that its absence favours chancroid. This teaching has caused many tragic mistakes. It should be emphasized that this induration indicates that a lesion has begun to heal, and its absence does not enable us to say that syphilis is absent too. Early chancres do not possess this clinical sign—not until they are six to ten days old. Similarly, chancroids (the old term “soft chancre” is misleading), when they become chronic, can also be indurated. In a series of 183 chancres on the labia majora only 17 per cent., and of 257 cervical chancres only 17.2 per cent., had circumscribed induration.¹ A more important but less frequent sign, almost diagnostic of syphilis, is oedematous induration. The tissues round the chancre are enlarged, painless, indiarubbery, and brawny. The hair follicles stand out, and the skin is thickened, and does not pit on pressure.

In the same series, oedematous induration occurred in 12.1 per cent. of chancres on the labia majora and in 7.2 per cent. of cervical chancres.

TREATMENT OF SYPHILIS

While watching *Spirochaeta pallida* for days on end by the dark-ground method, in the hope that I might obtain some clues about its morphology, its persistent behaviour in a certain way gave me a new conception concerning the treatment of syphilis. I found that *Sp. pallidae* bathed in salvarsanized serum gradually lose their normal appearance, become ghostlike, fragmented, and paralysed, and in about five days apparently die. Then, in the space of five or six hours, they recover their normal appearance, are revived, regain their spirals and motility, and become as normal and as active as their control spirochaetes which have not been similarly “doped.” This strongly suggests that arsphenamine should be injected at intervals of five days or less, instead of waiting the customary week, which gives the spirochaete three days in which to recover. It should be attacked with fresh drug when its vitality is lowest. In this way the largest number of spirochaetes are killed in minimum time, the survivors and resistant forms are destroyed sooner, and, what is equally important, they are prevented from multiplying, and are less likely to develop resistance to arsenic. With this scientific foundation I started a strong bi-weekly course of injections at the Whitechapel Clinic some three years ago. Some thought that the patients would not stand such doses, and that the percentages of fatalities and complications would be too high. This has not been our experience. My medical colleagues at the clinic are most enthusiastic about the course, and the results obtained justify this. The details are as follows.

WHITECHAPEL COURSE

First to fifth week: intravenous neoarsphenamine 0.45 gram weekly; bismuth 0.2 gram. Deep subcutaneous sulpharsphenamine 0.3 gram weekly; bismuth 0.2 gram.

Sixth to eighth week: mist. pot. iod. 5 to 15 grains, t.d.s., p.c.

Ninth to thirteenth week: repeat as during the first five weeks—namely, total arsphenamine, 7.5 grams, total bismuth, 4.0 grams, in thirteen weeks. Patient to report for blood test in seven days following last injection of course. To report again in twenty-eight days, and then to be given mist. pot. iod. until the next course begins. The weight of the patient, albuminuria test, and urobilinogen test are taken at each injection. A prophylactic draught containing liver extract conc. and glucose is swallowed before each injection. Each patient to receive three courses, with a rest interval between each course of eight weeks. At the discretion of the medical officer a course of intravenous injections once a week only, or deep subcutaneous injections once a week only, spaced as above, may be given to weakly patients—especially those over 45 years of age, or those with late syphilis.

This course was prepared primarily for those in the acute infectious stages, but it must be remembered that the patient's age is important. Those over 40 years eliminate drugs more slowly, and have more fibrous tissue in the liver, than do younger people. This strong course is therefore not so suitable for elderly patients.

Hitherto, practitioners have attempted to lessen the incidence of post-salvarsan jaundice and dermatitis by giving (1) smaller doses of the drug, (2) frequent intervals of rest between the doses, or (3) larger doses with correspondingly longer rest periods from treatment. These methods have had several serious disadvantages as a result of (a) lowering the therapeutic efficiency of the drug, (b) prolonging the course of treatment, (c) preventing many who would otherwise be cured from attaining that goal, because during the early and vital stages of treatment, when *Sp. pallidae* are most vulnerable, they have been irritated and not destroyed.

The excretion of arsenobenzene is rapid, especially when administered by the intravenous route. If it is too rapid the kidney and liver cells are liable to become damaged. This is more likely to occur if a single large dose of 0.75 gram or 0.9 gram is given. It is preferable to split this dose into two separate smaller doses of 0.45 gram and 0.3 gram, although these are given within the same period (generally one week) as the larger single dose. The aim of treatment is to kill *all* the infecting organisms with as little inconvenience and damage to the patient as possible.

In early syphilis, during the acute infectious stage, the dosage in the first week should be the strongest that the body can stand with safety. This same dosage should then be maintained—but not increased—each week throughout the course. Although arsenic is a cumulative poison, with time the body becomes habituated and more tolerant to it, and the tissues become accustomed to deal with it, *provided the dose is not raised*. The weekly dosage should be kept the same—that is, just beneath the threshold of intoxication—or damage to the liver cells, the most sensitive structures in the body to arsenic, will ensue. For the average patient this means 0.6 to 0.75 gram of neoarsphenamine per week. The deep subcutaneous method is therapeutically more efficient, safer, and causes fewer toxic complications than the intravenous route. In the Whitechapel course the methods alternate, so that the tissues are subjected to continual regular absorption of the drug over a long period, with as concentrated a dose as is consistent with no damage to the tissues.

The effects of treatment on the Wassermann reaction in 241 consecutive cases which completed the full course are given in the following table:

Whitechapel Course: Results of Treatment on the Wassermann Reaction

Type of Case	No. of Cases	Wassermann Reaction within a Month of End of First Course		
		Positive	Doubtful	Negative
Sero-negative primary ...	65	—	—	65 (100%)
Sero-positive primary ...	114	1 (0.87%)	1 (0.87%)	112 (98%)
Sero-positive secondary	62	2 (3.22%)	1 (1.61%)	59 (95.1%)
Total	241	3 (1.21%)	2 (0.82%)	236 (97.9%)

The treatment is most accurately judged by its effect on the secondary cases, as the whole body is in a state of syphilitic septicaemia in these patients. A negative Wassermann reaction occurred in 95 per cent. at the end of the first course. No "Wassermann relapses" have been observed.

It is now the fashion, for fear of arsenical complications, to lessen the amount of arsenic, and to rely more on bismuth, which is far below arsphenamine in efficiency. This, and the lessened use of mercury, is, I think, a backward step. A course of treatment cannot be estimated by the results of the Wassermann reaction alone; the percentage and severity of the complications must be included.

Complications with the Whitechapel Course

Type of Case	No. of Cases	Arsenical Dermatitis	Jaundice	Furpura	Per cent.
Sero-negative primary...	65	4 (6.15%)	1 (1.53%)	—	7.69
Sero-positive primary ...	114	5 (4.38%)	1 (0.87%)	2 (1.75%)	7.01
Sero-positive secondary	62	—	1 (1.61%)	—	1.61
Total	241	9 (3.73%)	3 (1.24%)	2 (0.82%)	5.8

An uneventful recovery followed all these complications. They are not confined to the period of the first course, but have occurred at any time after the beginning of treatment, and cover a period extending over two years. With this Whitechapel course we have had comparatively few complications; most of them have been mild cases of dermatitis (3.73 per cent.). Jaundice (1.24 per cent.) has given little trouble. Although 29,015 arsenical injections have been given during the past two years there have been only two fatalities. The percentage of complications has, I believe, been few because the course has only one rest of three weeks, and because the dosage remains the same each week. This decreases the liability of sudden shock to, and paralysis of, the liver. If rests are given too frequently the tissues become less accustomed to the arsenic at each rest, and have to re-establish their equilibrium and become re-educated to the drug. This, if it happens too frequently, lowers the general resistance of the body. It is a mistake, I think, to give a rest every two or three weeks, just as the body is becoming acclimatized to the drug and the spirochaete is being overcome. I should like to stress the need of a sufficiency of treatment. Two or three random injections of arsphenamine are inadequate, and destroy the patient's natural immunity.

At St. Thomas's Hospital I analysed the pregnancies of 300 syphilitic mothers before and after treatment. The figures are significant in this respect. Before treatment these 300 mothers had had 739 pregnancies, of which over 50 per cent. were unhealthy. After treatment their total number of pregnancies was 305, of which just over 9 per cent. were unhealthy. The mothers who had had under one course of injections—that is, less than 5 grams of neo-

arsphenamine—had 30 per cent. unhealthy pregnancies. Those who had received more than one course of injections had only 3.75 per cent. of unhealthy pregnancies. What a difference a few extra grams of organic arsenic made to these mothers, to their babies, and to their future!

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A SENSITIVE TEST FOR THE PURITY OF AVERTIN SOLUTION

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It is well known that avertin solution must be freshly prepared before use, at a temperature not exceeding 40° C. The reason for this is that, if overheated, or prepared too long before use, decomposition occurs, with the formation of dibromovinyl alcohol and hydrobromic acid, together with a further decomposition of the former into dibrom-acetaldehyde, according to the following equations:

The dibromacetaldehyde so formed is highly injurious to the mucous membrane of the rectum and colon, and cases of such injury have occurred, varying in severity from a mild post-operative discomfort to necrosis and sloughing of the colon, resulting in death.¹ In their original introductory article, Shipway and Blomfield² stated that the hydrobromic acid formed in the process of decomposition of avertin solution is at once detected by the Congo-red test. The experiments to be described prove that "universal indicator" (B.D.H.) is a more sensitive and reliable agent than Congo red as a test for the purity of avertin solution. These experiments were planned and carried out by Mr. Butchers, chief pharmacist, Manchester Royal Infirmary, and his chief assistants, Dr. Bullock and Mr. Priddy. The entire credit for the interesting and important discoveries which have been made is due to them, my own part being limited to the clinical application of their valuable work.

TECHNIQUE OF NEW TEST

Universal indicator gives the following colorations:

In the presence of	alkaline solutions (pH 8.0)—green
"	neutral " (pH 7.0-7.5)—greenish-yellow
"	acid " (pH 6.5)—yellow
"	" " (pH 6.0)—orange-yellow
"	" " (pH 5.5)—orange
"	" " (pH 4.0)—red

Transfer 3 mg. of prepared avertin solution to a clean test tube, and cool. In a similar test tube place an equal volume of the distilled water used in the preparation of the avertin solution. Add two drops of universal indicator to the contents of each tube. The colour of the avertin solution should be greenish-yellow, and it should not be possible to detect any difference in the colour of the contents of the two tubes. It is essential that the two test tubes should be scrupulously clean and previously rinsed with distilled water. The pH of ordinary distilled water may vary, and the actual sample previously used for the preparation of the avertin solution should serve as the control in the test. The above test is simple and rapid: if carried out as described it does not contain any fallacies. A possible theoretical objection is that greenish-yellow is a colour liable to varying individual interpreta-