we have had a ready response from the men. I personally have inoculated over 200 applicants, and have not seen a patient sick enough to go to bed; and at Fort Barrancas, Florida, where the men have constantly been more or less exposed to typhoid fever, there has not been a case for nearly two years among approximately 700 men; and while as yet they have not all been inoculated, yet many have, and each one protected helps to prevent somebody else from getting the disease.

The history of the use of antityphoid inoculation we know goes back to 1898, and to many of us it may seem strange that such a promising procedure has been used so little up to date; and yet it seems not to have been popular or widely used among hospitals in civil life, in institutions, or among gangs of men working on big jobs. One of the main reasons for this is the idea among the people—and I find this is so to quite an extent in the army, too—that it gives the patient a bad sore arm, makes him sick and really prostrates him. This is not true. Very few suffer at all from it, and it is not to be compared in severity with the ordinary reaction from smallpox vaccination.

CONCLUSIONS*

Now, therefore, considering all the data I have presented on the subject, it seems that the present status of these inoculations against typhoid fever is that they are valuable as a method of preventing the disease and are perhaps the most valuable single asset we have in combating an epidemic, and that there is surely no doubt in the minds of most thinking and up to date medical men that they should be used in the following classes of persons: first, all nurses, ward attendants, hospital corps men, red cross assistants, physicians and medical students; also all persons who contemplate a journey into a section where typhoid is known to exist or is suspected of existing. Also, the inoculations should be done generally in districts suffering from an epidemic, and especially in the families where a case exists, and I might add that in time of war all volunteers at camps of concentration should be inoculated as soon as possible after the camp is started.

Finally, it seems that typhoid will always be with us, but there is no necessity of its always being with us in our armies to any such appalling extent as it has in the past; therefore, the necessity for antityphoid inoculations will surely always be with us, for no matter how careful we are of our sanitation, our milk, our water, our flies, our contact infection, we will always have one or more of our much talked of friends, the chronic typhoid carriers, and it is only by inoculating them and other friends and acquaintances that we can keep more or less of them free from typhoid.

I am convinced of the harmlessness, and at the same time, of the effectiveness of this procedure, and would recommend its universal adoption, to the end that our armies in time of peace and war, and our communities at all times, may be kept as free as possible from that terrible epidemic disease, typhoid.

And last, but not least, I believe I can state from a careful study and investigation of the matter that the present status of antityphoid inoculation as a means of prevention is assured, and that its future possibilities are great.

* Nearly 1,000 additional cases have been inoculated since this article was prepared, with about the same results; and Colonel Leishman's recent lectures before the Harben Society show, I believe, the same good results in the very latest work in the British Army.

THE TREATMENT OF SYPHILIS WITH EHRlich's "606"*

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PART I. THE THEORETICAL AND EXPERIMENTAL BASIS FOR THE USE OF "606"

The object of experimental chemotherapy is the preparation and discovery of drugs which shall possess specific powers over given parasitic micro-organisms. The pursuit of this object has recently been greatly promoted by the discovery by Professor Ehrlich of a drug which possesses extraordinary power of destruction over certain, at least, of the parasitic spirochetes. Ehrlich has for many years been engaged in the synthesis of drugs, the ultimate purpose of which was the destruction within the body of such parasitic organisms as trypanosomes and spirochetes under conditions in which the organic cells of the host would be left unaffected. In other words, and to use Ehrlich's terminology, it was necessary to seek drugs which were on the one hand highly parasitotropic and on the other were quite devoid of organotropic activities. In the course of this quest, Ehrlich has had the good fortune to produce a number of drugs which more or less fulfilled these ideal conditions, but recently the quest has been crowned with an extraordinary achievement that promises to be of the greatest importance in the treatment of syphilis and hence of incalculable benefit to the human race.

We may begin by summarizing a fragment of the conceptions which led Ehrlich to his most recent important discovery: The animal parasites causing malaria, trypanosomiasis, syphilis, amebic dysentery, etc., apparently can not be successfully attacked by means of immune sera, and therefore their conquest must be attempted by means of ordinary chemical substances. The history of the treatment of malaria with quinin indicated that this line of attack is a feasible one, particularly in view of the fact that quinin represents the successful employment of one drug out of an innumerable series tried by man in nature. It is possible through the aid of modern synthetic chemistry to prepare an almost infinite number of combinations which can then be tested on animals infected with the animal parasites of the diseases named, until compounds are found which exhibit a higher degree of poisonous effect on the parasite than on the host. Having achieved this first selection, the partially successful compound can then be further altered by possible substitutions, which may serve to render it still more suitable for the purposes in view.

While Ehrlich was engaged in developing this line of investigation, the substance atoxyl, which is an empirical arsenical compound, came into use in the treatment of sleeping sickness, for which it proved a highly useful although not invariably successful drug. This substance, which was demonstrated to be more poisonous for one of these animal parasites than for the human host, became the starting point for chemical variations which culminated in the preparation of the compound "606."

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The starting point of the successful substitutions in connection with atoxyl was the working out of its real constitution. It had been considered as an anilid of arsenic acid,

which, being an unstable compound, would not allow of the necessary chemical manipulation and substitution. In collaboration with his chemical assistant, Bertheim, Ehrlich ascertained that atoxyl is in fact the sodium salt of para-aminophenyl arsenic acid,

In this compound the molecule of arsenic is firmly attached to the benzole ring, because of which the compound admits of the necessary manipulation and substitution at different positions in the ring. Different substitution products were next prepared and tested for their therapeutic effects on infected animals. Up to the present time, about 630 substitution products have been made and tested, of which four only have proved to possess the requisite parasitotropic properties, without at the same time being injurious to the organs of the host. These substances are: acetyl-atoxyl; arsenophenylglycin, or "418," trypanosan, and arsenobenzol, or "606." Excepting the drug trypanosan, arsenic is the active principle in all the preparations, the other chemical groups present merely serving to fix this substance to the parasite. Thus for example it has been found that the acetyl group has a special affinity for trypanosomes and the amino and hydroxyl groups a special affinity for the spirochetes.

It is obvious that this kind of pharmacologic research is possible only if animals can be used as the basis of experiment. Fortunately, the discovery of the transmissibility of syphilis to the lower animals and of *Treponema pallidum*, the parasitic cause of syphilis, came to be achieved about this time. Hence the new drugs could be tested not only against fowl spirilla and the spiral organisms of relapsing fever, but also against *Treponema pallidum* in infected rabbits. In due time preparation No. "606" came thus to be tested, and was proved to be efficient in a single dose, which while it sufficed to destroy all the parasites was without perceptible injurious effect on the host.

In the course of previous investigations, Ehrlich had ascertained that it was not safe to attempt to destroy the animal parasites by means of repeated small doses of an injurious drug, and for the reason that in the course of this method of treatment, the parasites often develop a toleration for the drug which they transmit to their progeny. The goal, therefore, became the discovery of a drug which in a single dose would destroy all the parasites, leaving the host uninjured, and this extraordinary achievement apparently is accomplished by "606."

EHRLICH'S THERAPIA STERILISANS MAGNA

The drug having been proved by repeated tests on animals to be without injurious effect it was next tested on human beings. The first to submit to inoculation were the assistants, since which time several thousand persons suffering from various forms and consequences of syphilis have been treated.

The reports which are appearing at present in practically every number of the important German medical weeklies from different parts of Germany and Austria are almost unanimous in their testimony to the remarkable effects of the drug in syphilis. In all but a few exceptional instances a single dose of the drug has sufficed to bring about a rapid disappearance of the lesions of syphilis and equally rapid improvement in the general condition of the patients. In the few instances in which these rapid effects were not achieved the dose of the drug, which was originally given was, as is now established, too small, and in many of these cases a second and larger injection has brought about the desired result. It is noteworthy that in many instances the patients who have improved rapidly after an injection of this drug had resisted the application of mercury sometimes over many months, or possessed idiosyncracies which made the use of mercury difficult or impossible. Thus far, a special idiosyncrasy against the drug has not come under notice. It is as yet too early to determine whether the patients who have responded so rapidly and perfectly to the administration of the drug as apparently to have been cured of this otherwise chronic disease by a single injection may ultimately suffer relapses. On the other hand many scores of patients have shown no relapses in the several months which have elapsed since the injections. What is highly important in the interests of prophylaxis is that within twenty-four or forty-eight hours of the injection of the drug superficial lesions, such as mucous patches, condylomata and primary lesions are freed from living spirochetes. This remarkable effect of the drug on the parasites can be readily demonstrated on the testicular spirochetal lesions of the rabbit, in which the innumerable spirochetes can be entirely immobilized within twenty-four hours with a single injection of the drug, after which the lesion quickly resolves.

ADMINISTRATION OF THE DRUG

The chemical name of "606" is paradiamidodioxo-dichlorarsenobenzole.

The substance is a yellowish powder which rapidly oxidizes on exposure to air, and is therefore put up in vacuum tubes. It dissolves in water with difficulty, making a strongly acid solution. As the acid solution is very painful, the substance is administered either as a neutral base (Wechselmann) or as an alkaline salt (Alt). The administration is by injection deep into the muscles, or into the veins or beneath the skin. At first, the administration was made either deeply into the muscles of the buttocks or into the circulation, but at present it is recommended that the administration be made subcutaneously according to the method of Wechselmann.

According to this method, the drug, in a dose which has varied up to the present from 0.3 to 0.6 grams, is dissolved in a mortar in 1 to 2 c.c. of ordinary solution of sodium hydrate. Acetic acid is then added, drop by drop, until the base precipitates out in the form of a fine yellowish suspension. This precipitate is collected in

subdivide the precipitate as finely as possible, which can be done by rubbing. The suspension is then drawn into a suitable syringe and injected subcutaneously below the shoulder blades after previous cleansing and disinfection of the part. It often happens that there is slight pain lasting a few minutes following the injection, and in

TABLE OF RESULTS OF USE OF EHRLICH'S 606 IN SYPHILIS

No.	Age.	Sex.	Infection.	Previous Treatment.	Condition Before Injection.	Injection.	Local Effects.	Condition After Injection.	Serum Reaction.	Remarks.
1	25	M	1/10, chancre; 2/10, secondaries	11 injections 1 gr. Hg Sal.	General secondary eruption; enlarged lymph nodes; serum ++	5/12/10; 8 c.c. each buttock. 0.3 gm. 606, not completely dissolved. Alt method.	Induration for 7 days, slight pain.	No improvement in 3 weeks.	6/16/10+35 days.	Small dose, resumed mercury.
2	38	M	1905, chancre and secondaries.	Irregular....	Tertiary syphiloma of back and chest; serum ++	5/12/10; 8 c.c. each buttock. 0.3 gm. 606, not completely dissolved. Alt method.	Marked induration, 7 days. scaly erythema of hands and feet.	Slight improvement in 3 weeks.	6/10/10+29 das.	Small dose, resumed mercury and KI; drug eruption.
3	21	M	3/1910, chancre; 5/1910, secondaries.	Only local treatment.	Circinate syphilid of face; macular syphilid of trunk; enlarged lymph nodes; serum ++	5/16/10; 0.3 gm. 606; 8 c.c. each buttock. Alt method.	Induration of buttocks for 7 days.	After 8 dys. lesions gone on face, and faint on body.	5/23/10+7 days.	Left hospital 5, 24, '10, considering himself well. Could not be traced.
4	32	M	5/1907, chancre and secondaries.	More or less constant; liquid.	Scaling syphilid of palms severe. Serum ++	5/16/10; 0.3 gm.; 12 c.c. each buttock. Alt method.	Induration lasting 7 days, slight fever 2 days.	50% improvement in palms after 7 days. Completely healed in 1 month.	6/10/10--25 days.	Began to work a orderly in hosp. 6/6; apparently cured by single injection. See Photographs Figs. 1 and 2.
5	20	F	4/1910, secondaries.	4 grs. Hg Sal. by injection	6 mos. pregnant; faint eruption. Serum +	5/19; 0.3 gm. 606; 10 c.c. each buttock. Methyl alcohol.	Marked induration 5 days, urticarial eruption 2 days.	Apparently well in 21 days.	6/28 - 30 days....	Aborted 5/29; fetus badly macerated, could not be obtained for examination.
6	24	M	10/1909, chancre; 12/1909, secondaries	Mercury in pill form for several months.	Severe rupial lesions, face, head and arms; hysterical. Serum ++	5/19; 0.3 gm. 606; 10 c.c. each buttock. Methyl alcohol.	Slight induration 4 days.	Marked rapid and progressive improvement. Lesions healed in 30 days.	8/30 - 3 mos. 11 days.	Gained 12 pounds. No recurrence in 3 mos. Photograph Figs. 3, 4.
7	51	M	1882, chancre and secondaries.	10 days treatment in 1882.	Ulcerating syphilid of knee and leg. Serum ++	5/23; 0.3 gm. 606; 10 c.c. each buttock. Methyl alcohol.	Marked induration of buttocks 7 days.	Sinuses closed induration gone and lesions of light color 21 days.	6/10 - 21 days....	Apparently cured.
8	25	M	10/1909, chancre; 1/1910, secondaries	2 grs. Hg Sal. by injection	Mucous patches, fading follicular syphilids of body. Serum +	5/23; .03 gm. 606; 10 c.c. each buttock. Methyl alcohol.	Slight induration.	Marked improvement, lesions gone in 2 weeks.	6/11 - 19 days....	Apparently cured by single injection.
9	23	M	5/1909, chancre; 9/1909, secondaries	"1 bottle of medicine."	Severe extensive pustular and tubercular syphilids of face and shoulders. Serum ++	5/26; 0.3 gm. 606; 10 c.c. each buttock. Methyl alcohol.	Induration of buttock 5 das.	Marked improvement. Lesions dry and faint in 14 days.		Gain in weight. Left hospital and could not be traced.
10	24	M	1907, chancre and secondaries.	KI 7 months	Severe periostitis, left tibia. Serum +	6/2; 0.3 gm. 606; 10 c.c. each buttock. Methyl alcohol.	Marked induration 7 days.	Pain and swelling disappeared in 8 days.	8/30 - 3 mos.	No recurrence in 3 mos.
11	28	M	1/1910, chancre; 5/1910, secondaries	No treatment.	Mucous patches and macular eruption on face and legs. Serum +	6/2; 0.3 gm. 606; 10 c.c. each buttock. Methyl alcohol.	Induration 7 days.	Face and leg clear in 7 days.	6/23 - 21 days....	Apparently cured by single injection.
12	22	M	4/1910, 3 chancres on lips; 5/1910, secondary eruption.	2 grs. Hg Sal. hypodermically.	3 large indurated chancres on lips; erythematous papular eruption on body. Serum ++	6/2; 0.3 gm. 606; 10 c.c. each buttock. Methyl alcohol.	Induration of buttock 5 days.	Chancre gone, eruption very faint; 21 days.		Great improvement in general condition. Photograph Figs. 5, 6. Could not be traced after leaving hospital.
13	29	M	1905, chancre and secondaries.	Treated 4 wks. in hospital. 1905; 1908, 8 weeks in hospital.	Arthritis of knee, broken down glands of groin, emaciated, anemic. Serum +	6/7; .03 gm. 606; 7 c.c. each buttock. Methyl alcohol.	Slight induration.	Marked and rapid improvement in general condition and lesions in 10 days.	6/30 - 23 days....	Apparently cured; 8/30 working as longshoreman; has gained 30 lbs.; serum -
14	20	F	6/1910, chancre and secondaries.	No treatment.	Mucous patches, general eruption. Serum.	6/7; 0.3 gm. 606; 7 c.c. each buttock. Methyl alcohol.	Induration 5 days.	Eruption and sores disappeared in 10 days.		Left hospital and could not be traced.

from 1 to 2 c.c. of sterile distilled water, and there are added either 1/10 normal sodium hydrate, or 1 per cent. acetic acid, as needed, until the reaction becomes precisely neutral to litmus. According as the reaction is or is not accurately neutral the injection will be followed by much, little or no pain. It is moreover desirable to

some instances a slight swelling arises on the second or third day following the injection, but no bad effects are produced. There may be slight rise of temperature and in some instances an urticarial eruption has occurred, but no specific toxic effects on the eyes, kidneys, or nervous system have been observed.

PERSONAL OBSERVATIONS

Although the number of cases to be reported on at present is small, the results have been so striking, and are in such accurate accord with the several thousands of cases reported from Germany that it has seemed desirable to make this report, especially because it is probable

one-half of the dose now being employed abroad. Hence it would not be surprising if in this first group relapses occurred. If so it would be both safe and desirable that a second and larger injection be given.

The efficiency of the drug is dependent in part on the dose employed. Hata has permanently cured all rabbits having spirochetal lesions by means of a single dose of an adequate size. We have found that when the dose is too small, relapses occur in the infected rabbits. Hence now that it has been determined that a dose of 0.6 gram is non-toxic for human beings, it is probable that the average dose will approach that quantity. At present, European observers are employing doses varying from 0.45 to 0.3 gram.

The drug is not generally available at the present time. The output is too small for general distribution, and Ehrlich has therefore up to the present been able to supply it to relatively few physicians, whose employment of it has also been in the nature of tests of its value. The final word concerning its value will not of course be said for a number of years, but the fact remains that we possess no drug the extraordinary effects of which in syphilis equals that of "606."

Fig. 1.—Scaling syphilid of palms. A. K. Duration of infection, three years; of palmar lesions, one year. May 16, 1910, 0.3 gm. 606. Wassermann before treatment, ++; June 10, 1910, negative; Sept. 1, 1910, still negative. (See photograph after treatment.)

that the drug will come to be extensively used throughout the United States. The patients were all in the City Hospital on Blackwell's Island, in the skin and venereal wards. The clinical diagnoses were all definite and unmistakable, and the serum reactions which were made regularly were conducted with the Noguchi modification of the Wassermann method.

In injecting the preparation into the first two patients considerable difficulty was experienced in getting the powder into solution, and the full dose of 0.3 gram which it was intended to administer was therefore not given. As we now know, 0.3 gram is a submaximal dose. These patients were injected before the method of Wechselmann had come into use, and even before the earlier modification of the original "Alt" method of preparation suggested by Ehrlich had been published. As a result no marked improvement occurred and the patients were put back on mercurial treatment. The remaining twelve received the full dose intended, and included examples of primary, secondary and tertiary lesions. The effects were in these instances truly remarkable and now, from three to four months after the injections relapses have not been observed to occur. Before the treatment the serum reactions were all positive and at the expiration of the time mentioned, in all the patients who could be traced, they have become negative. Aside from the temporary local disturbance caused by the injection in some instances, no untoward symptoms were observed, except an urticarial eruption in two of the cases. None of the patients received more than 0.3 gram, which is about

Fig. 2.—Scaling syphilid of palms. A. K. Condition of palms two weeks after treatment with 606. (See photograph before treatment.)

The one drug with which it may be compared is quinin, which in many instances is so highly efficient in the treatment of malaria, but even there a single dose does not suffice to destroy all immediately visible parasites, as does an adequate dose of "606."

PART II. THE USE OF "606" FROM THE STANDPOINT
OF THE CLINICIAN

Personal experience in the treatment of syphilis has convinced us that mercury given in the early stages in as large doses as the system will tolerate insures the patient more certainly against relapses, and that patients who are treated by small doses over long periods of time in the manner which is still too often employed by even the best known syphilographers sometimes develop in the patient thus treated an immunity to the drug which renders it comparatively inert. This latter class of patients not infrequently become the subjects of obstinate relapsing lesions of the skin and mucous membrane or, later, the victims of paresis, tabes, or other visceral affections. Professor Ehrlich's contention, therefore, as to the value of a drug which at one dose destroys the invading organism is supported by clinical experience in the use of mercury. It is true that the methods of administering the latter have been greatly improved in the last few years, as is witnessed by the greater fre-

treatment by the Wassermann reaction cannot be too strongly emphasized, showing as it does that in the past some patients may have been greatly overtreated while the majority have received too little of the specific drugs. It is well known that there are certain cutaneous and general manifestations of syphilis which respond slowly or not at all to mercury even in heroic doses. Among these may be mentioned certain scaling syphilids of the palms, chronic nodular syphilids in patches of the type which clinically resembles lupus vulgaris, certain forms which affect the flush area of the face and bear a marked clinical resemblance to lupus erythematosus; also mucous membrane affections like leucoplakia, chronic interstitial glossitis and relapsing deep and superficial lesions of the tongue and throat. Aside from these lesions which are under direct observation there are the so-called parasymphilitic manifestations, such as tabes, the treatment of which by the classical drugs leaves much to be desired. In malignant syphilis with early destructive lesions and the development of profound cachexia,

Fig. 3.—Nodular and ulcerating syphilid. W. C. N., date of luetic infection, October, 1909. Rupial and fungating lesions of face and arms of six months' duration. May 19, 1910, received 0.3 gm. 606. Wassermann before treatment, ++; Aug. 30, 1910, negative. (See photograph after treatment.)

Fig. 4.—Nodular and ulcerating syphilid. W. C. N. After treatment with 606. (See photograph before treatment.)

quency with which it is employed hypodermically and by inunction, but our present means are still too often slow or inefficient in their action especially in the early stages. Delay or insufficiency in the amount of mercury at this time permits the entire system to become infected by the *Treponema pallidum* and damage to the blood-vessels or important structures takes place which might be prevented by energetic treatment. It will generally be conceded by physicians who come in contact with a large number of syphilitics that while mercury and potassium iodid are efficient in the great majority of cases in controlling the manifestations of the disease, there are certain intractable cases in which they fail to control the symptoms either on account of idiosyncrasy to one or both of these drugs or other causes. Furthermore, owing to the length of time required in treating a case of this infection patients often become discouraged and cease medication after a few months or a year or two. The great advance made in controlling the

mercury, moreover, often fails to do good and not infrequently does harm. When, therefore, Dr. Flexner, of the Rockefeller Institute, in the early part of May, this year, received a supply of the new preparation "606" and asked to be allowed to try it in a number of selected cases in the City Hospital, the proposition was received with favor and the patients in the skin and venereal wards were placed at his disposal. At that time the experience in the use of the drug had been rather limited and the patients who were treated were carefully selected as free from organic disease of the kidneys, heart or eyes; in fact, all the contraindications for the use of the drug, as stated by Prof. Ehrlich, were carefully observed. The patients were also informed that a new drug was about to be employed which would cause them a considerable amount of pain and was yet in the experimental stage. There was no difficulty in obtaining their consent, and the most striking testimony as to its value in the treatment of obstinate cases of lues was furnished by other patients in the wards, who on seeing

the results accomplished by its use repeatedly asked that it be given to them.

The rapid action of arsenobenzol in cases of obstinate syphilis of the palms is strikingly illustrated in Figures 1 and 2.

Patient, aged 32, had a genital chancre three years before, which was followed by the usual secondary symptoms. Following his infection he had taken medicine in "liquid and capsule" form almost continuously. The eruption on his hands was of one year's duration. The Wassermann reaction was strongly positive. On May 16, 1910, he received 0.3 gm. "606." Two weeks afterward his palms presented the appearance shown in Figure 2 and in another fortnight he was entirely well.

The result obtained by the use of "606" in this case was far more rapid than any which we have seen after the use of mercury. Furthermore, after an apparent cure from mercury in these cases of chronic palmar syphilis the majority relapse within a few weeks to a month or two, whereas this patient had had no recurrence up to

obtain complete resolution under several weeks to two or three months; in fact, the induration sometimes persists for a year or longer. As these extragenital initial lesions are a source of great mental distress to the patient and one of danger to his environment, their rapid retrogression under this remedy surpassed the result which could have been expected from mercury.

Figures 3 and 4 illustrate a rather malignant form of eruption which occurred less than one year after infection:

Patient, aged 24, contracted syphilis in October, 1909. A month later a pustular eruption appeared first on his face and then on the body. The lesions become rupial and afterward assumed a fungating type. He also suffered from sore throat, headaches and osteocopic pains. From October up to the time he entered the hospital he had taken mercury in pill form. On May 19, 1910, he received 0.3 gm. "606." There was a perceptible change after a week; the patient's general condition improved and in two weeks he gained 9 pounds.

This form of early malignant syphilis, which indicates low resisting power on the part of the infected

Fig. 5.—Multiple chancres. J. S. C., infection two months ago. Two chancres on upper lip and one on lower in median line; papulo-erythematous eruption on body. June 2, 1910, 0.3 gm. 606. Wassermann before treatment, ++. (See photograph after treatment.)

September first and the Wassermann reaction has remained negative.

In the case of multiple initial lesions of the lip (Figures 5 and 6) of two months' duration, with secondary manifestations of the skin, complete resolution of the chancres took place within about ten days, leaving practically no evidence of their former existence. The entire appearance of the patient, too, underwent a marked change, as before treatment he was anemic, depressed, and evidently showing considerable constitutional disturbance from his infection. The great improvement which took place in his general condition after the injection continued up to the time he left the hospital. The Wassermann reaction at that time was negative. The duration of the initial sclerosis under mercurial treatment is a very variable one. It is unusual, however, to

Fig. 6.—Multiple chancres. J. S. C. After treatment with 606. (See photograph before treatment.)

individual, sometimes fails to respond to mercury. The almost magical result which followed the use of "606" is illustrated in Figure 4 which was taken about two weeks after the administration of the drug. Up to September 1 the patient had remained well and showed a negative Wassermann reaction.

The cases just referred to are examples of the most brilliant results obtained. In the table additional data are given bearing on the other cases which were treated at the City Hospital. Through the kindness of Dr. Flexner, we have been able in the past month to secure a sufficient quantity of the remedy to treat several private patients who are still under observation; the cases will be reported in greater detail later. One of these was a case of rapidly progressing optic neuritis with tabetic symptoms, the result of a specific infection twenty years before:

Patient, referred by Dr. Marks of Frankfort, was a man, aged 38, in whom it was noticed two and a half years ago

that his pupils were smaller than normal. Shortly afterward, he developed a diplopia which was diagnosed by the ophthalmologist as paralysis of the right abducens and beginning atrophy of the optic nerve. From that time until August 1 he had been under active mercurial treatment but without benefit. His vision since April, 1910, has been rapidly diminishing and he has concentrically contracted field, Argyll-Robertson pupil and partial atrophy of both optic nerves. Although we recognized that affections of the optic nerve are given as a theoretical contraindication to the use of "606," still at the urgent solicitation of the patient and his friends the drug was administered, but he was told beforehand that very little result was to be hoped for. A dose, 0.45 gm., was prepared after the method of Wechselsmann and injected beneath the right shoulder blade. This was followed by severe pain which persisted for three or four days and had to be controlled by several hypodermics of morphin. On the second day, a marked swelling appeared at the site of injection which began to resolve at the end of a week. At no time was there any evidence of softening. The patient's temperature rose slightly on the second day reaching 100.4 F.; his pulse was rather high for the first week varying from 90 to 110 and he developed considerable physical weakness. Although little result was expected from the drug in this case, the patient is under the impression that the rapid progress of the disease has been arrested.

In the following case of cerebral syphilis an improvement took place in spite of the symptoms which mercury and other medication had failed to influence:

Patient was a man, aged 38, whose infection dated back six years. In February, 1910, the neurologic examination made by Dr. M. G. Schlapp was as follows: "Pupils unequal, the right being larger; they react to light, not to accommodation—very nearly Argyll-Robertson condition. Speech thick, not truly scanning. General involvement of the muscles of the pharynx, tongue and face on right side; anesthesia in the same area. Partial paralysis in the right leg. Foot dragged in walking; weakness in the leg is sufficient to prevent standing on it. Babinski sign pronounced; clonus in both knee and ankle, the whole leg anesthetic." In spite of vigorous mercurial and iodine medication there occurred an increase in symptoms and area involved in June, 1910, while staying in England. The patient lost consciousness on several occasions; he also had facial paralysis complete for a time on the right side. Both legs developed weakness and anesthesia (patient's statement). A similar attack occurred in July, 1910, after a slight improvement, again involving both legs and right side of the face. Incontinence of urine marked. Under 43 injections of a mercury arsenalate, 20 inunctions and a daily dose of 3 grams of sajodin, rest and hydrotherapy, sufficient improvement occurred to enable the patient to get about.

On August 31 he was given an injection of 0.45 gm. "606" subcutaneously. A Wassermann reaction on this day was positive. Absolutely no pain followed this injection, nor were any unpleasant effects of any kind experienced except the induration which persisted for ten days. Improvement was noted on the day following the injection and he left the hospital on the second day, remaining in bed, however, in his home for two or three days longer. On the day succeeding the injection the patient stated that the mental depression from which he suffered weeks before had become materially less, his facial paralysis showed improvement and his speech disturbance was less marked.

A second examination made by Dr. Schlapp on September 9, nine days after the injection of "606" is as follows: "Pupils in same condition as at first examination. Incontinence has ceased. Paralysis of face and speech muscles has improved; anesthesia the same as at first examination. Right-sided sweating of the face, neck and upper part of the trunk. Both legs show Babinski sign, ankle and knee clonus, indicating extension of the process since February. There is, however, a noticeable decrease in anesthesia and muscular weakness. Diagnosis: Syphilitic obliterating endarteritis of the base, involving both pyramidal tracts and the sympathetic."

The patient was kindly referred by Dr. James C. Johnston, under whose care he is at present. A further report will be made at a later date. (September 21, Wassermann reaction still + —.) The absence of pain in this case was probably due to greater experience and care in preparing the remedy. It is important to emphasize the necessity of thoroughly rubbing the precipitate which follows the addition of acetic acid to the caustic soda solution until a homogeneous paste is obtained. The neutralization of the mixture should then follow and the latest technic as given by Wechselsmann¹ observed.

The question of danger in the use of the new drug is one that should be touched on. It would be a marvel should a drug so potent as this one in the destruction of living parasites within the body be wholly devoid of injurious or secondary effects on the organs. We possess indeed no really pharmacologically active drug for which there may not exist contraindications and from which secondary and objectionable effects have not been noted. Certainly neither mercury nor iodine of potassium form exceptions to this rule. The remarkable fact about "606" is that in the several thousand cases in which it has already been employed, and considering the wretched physical state in which many of the patients were at the time of the injection, so very few untoward effects have occurred. It is now clear that the mode of administration is important, and especially the elimination of the methyl alcohol used at an early period to dissolve the drug, since this substance may produce unpleasant if temporary symptoms, as in the three cases reported by Bohac and Sobotka.² The result in a case of Hoffmann's³ in which a central embolic pneumonia, terminating in recovery, followed an intragluteal injection, was probably analogous to the condition of the lungs which may follow from an intramuscular injection of insoluble mercurial salts when the needle has inadvertently penetrated a vein. Ehrlich has warned against the administration of the drug to weak patients suffering from advanced cardiovascular disease, and the wisdom of this precaution has been emphasized by the two accidents encountered at the Charité in Berlin and the neurologic clinic at Bonn. Ehrlich further warns against the use of the drug in cases in which lesions of the optic nerve exist, and urges that in doubtful cases an ophthalmologic examination be made. Finally, it has just been announced that a further improvement in the preparation of "606" has been made which still further reduces the toxicity—indeed it is stated to be one-third that of the older substance. To this preparation Ehrlich has given the name "hyperideal."

From the collective reports of those who have used the drug the impression is gaining that we have in arsenobenzol a most thorough agent in controlling the manifestations of syphilis which are caused by the presence of the treponema. It may reasonably be hoped, therefore, that all the lesions which depend on the presence of the organism will be favorably influenced and the most we can expect in the secondary degenerative changes is that the process may become arrested. Further experience with the drug will determine with more accuracy the dose which is necessary to bring about a cure, the time that must elapse before a second dose can be safely given and the more definite indications for its

1. New York Med. Jour., Sept. 3, 1910, p. 449.

2. Wien. Klin. Wchnschr., July 28, 1910.

3. Med. Klin., Aug. 14, 1910, p. 1201.

use after relapses or failure of a single dose to control the symptoms.

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Position Assumed by Patient in Ear Disease.—According to W. E. Chamberlain in the *Ohio State Medical Journal*, in case of nystagmus of otitic or cerebellar origin the position of the patient in bed is of interest and easy of explanation. With a circumscribed inflammation on the right side and with it a nystagmus to the right, the patient lies on the right side with the head buried in the pillow. In this position, the eyes are turned involuntarily toward the left and the nystagmus and dizziness are decreased. Let now a diffuse suppuration follow the circumscribed or let the right labyrinth be removed by operation, then the patient does not lie on the right but on the left side, for in this position the eyes are directed to the right. The nystagmus and dizziness, most extreme with vision toward the left are decreased by looking in the opposite direction. Placed in the Romberg position, a patient with nystagmus to the right will fall to the left and *vice versa*. In other words, he falls in the direction of the slow component.

CREATININ AND CREATIN METABOLISM IN CHILDREN *

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In a lecture, delivered before the Harvey Society two years ago, Folin¹ said:

I venture to predict that we shall learn more concerning the abnormal or subnormal metabolism of the sick on the basis of creatinin and creatin determinations alone than could be learned in another thirty years by means of the nitrogen determinations of the past.

Creatin is methyl guanidin acetic acid and may be converted into creatinin by the withdrawal of one molecule of water. It would seem remarkable that creatin, which is the most important of the extractives of muscle and the chief constituent of broths and beef extracts, and creatinin, a constant constituent of the urine, should have received so little attention in clinical medicine. This seems to be even more striking when we consider that uric acid, which appears usually in smaller quantity, both absolutely and in nitrogen content, in human urine, has been the subject of so much discussion.

The explanation lies in the fact that the older method of determination, which depends on the precipitation of creatinin with zinc chlorid, was very tedious and unreliable. It was in 1904 that Folin² published his accurate and simple method of determination which has given such an impetus to the study of creatinin and creatin metabolism. Folin's method depends on the fact that creatinin gives, with picric acid and sodium hydrate, a brownish-red color which cannot be distinguished from that of a potassium bichromate solution. The urine is treated with the above reagents, in proper quantity, and the resulting depth of color compared with that of a half normal bichromate solution. The degree of color produced is read off on a colorimeter and the creatinin content is thus given. Creatin may be estimated by boiling it with normal hydrochloric acid, thus converting it into creatin, which latter is then determined as above.

Evidently the creatin and creatinin excreted may come either from the food taken in or from the metabolism within the body, exogenous or endogenous. On a creatin- and creatinin-free diet Folin was able to show that normal persons excrete creatinin but no creatin. Creatin given by the mouth, unless fed in large quantities, does not appear in the urine, and then in part only. The administration of creatin was found to have no effect on the amount of creatinin excreted.

Both Folin³ and Hoogenhuyze and Verploegh⁴ were able to demonstrate the very interesting fact that, although the creatinin excretion differs in different subjects, a given individual, under normal conditions, excretes a remarkably constant amount of creatinin. This is so constant, in fact, that at one time Folin was able to trace the loss of urine from a twenty-four-hour specimen because of the drop in the creatinin content.

* Read in the Section on Diseases of Children of the American Medical Association, at the Sixty-first Annual Session, held at St. Louis, June, 1910.

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1. Folin: THE JOURNAL A. M. A., May 2, 1908, p. 1391.

2. Folin: Ztschr. f. physiol. Chem., 1904, xli, 223; and Am. Jour. Physiol., 1905, xlii, 48.

3. Folin: Festschrift f. Olof Hammarsten, iii, Upsala, 1906.

4. Hoogenhuyze and Verploegh: Ztschr. f. Physiol. Chem., lvii.