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THE VALUE OF THE STAINED VAGINAL SMEAR IN GYNECOLOGICAL DIAGNOSIS

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The history of gynecological diagnosis has been divided and the characteristics of the successive eras have been shaped by a series of discoveries, inventions, and methods. The vaginal speculum, the uterine sound, bimanual pelvic examination, the uterine curette and other tissue sampling technics, bacteriological examination and tubal insufflation with x-ray visualization, all have added to the possibilities of observation and deduction. Each has made a contribution appropriate to its sphere of application. The essential usefulness of each contribution has required many years to assay, and not infrequently new methods have, in the course of events, modified the importance of older ones.

The purpose of this paper is to describe what we know of a new method of diagnosis as it may be applied to the field of gynecology as a whole. The stained vaginal smear as a laboratory entity is not really new for Papanicolaou has been studying it for many years, first in animals and more recently in the woman; however, in its interpretation and in its readiness for practical application it is new, for it has only been in the last few years that the effects of pathological processes have been sufficiently shifted from the normal variations of the cells to make application of the procedure of practical value to the diagnostician. Either fortunately or unfortunately, we have been led to think of the vaginal smear chiefly from the point of view of the diagnosis of uterine cancer. This may be justifiable, because the record of the method in revealing early cancer lesions cannot be approached by any other means. However, this interest in cancer has seemed to hide the fact that the procedure can reveal many other normal and pathological processes occurring in the utero-vaginal tract. Our experience in New York, and more recently in San Francisco, has led us to feel that it should become a part of the routine gynecological examination almost, if not quite as essentially, as the use of the speculum or manual palpation. Certainly it is more important than routine blood examinations, urine analyses, or Wassermann tests. The

variety of information it is capable of giving should place it at the top of all laboratory-involving procedures as far as the gynecologist is concerned, for it reflects normal physiological states, as well as the pathological, with a fidelity which would seem to indicate it as indispensable. The only close analogy to it from the general clnical point of view is the study of blood smears. Hematology has become an indispensable adjunct to internal medicine. The study of vaginal smears can become an even more important asset to the gynecologist. It would seem almost certain that, in time, this procedure would become as definite a part of the routine of gynecological diagnosis as bimanual palpation For this reason we feel that this method should be brought to the attention of all physicians caring for women patients We have learned to anticipate and have learned to interpret the results from blood examinations; indeed, no physical examination is considered complete without such a study. The same attitude should prevail with regard to the more specific gynecological examination.

Principles of the Vaginal Smear Technics

Exfoliation of cells from the epithelial surfaces of the endometrium, endocervix, portio and vagina occur normally as an expression of the hormonal stimuli of the ovarian secretions. These cells drift downward and collect in the fornix of the vagina, where they remain for sufficient periods of time unless artificially disturbed so that one may recover them and by placing them upon a glass slide can study their characteristics. The size, shape, intracellular characteristics and staining reactions of the cells change with the various ovarian stimuli of lack of them, to which they have been subjected, so that one can tell the preovulatory phase from the postovulatory, the menstrual and post-menstrual almost as surely as though one were examining an endometrial biopsy. And of course very much more easily and simply, for the vaginal smear can be an office procedure without invasion of the uterine cavity. In like manner catamenial changes, the menopause and even pregnancy may be suggested by evidences of considerable certainty.

In abnormal states such as infections of the endometrium and endocervix, trichomonas and monilia vaginitis, hyperplasia of the endometrium, uterine polypi, as well as cancer, the vaginal smear exhibits cellular characteristics which are not only suggestive but more and more often diagnostic. The cervical mucus acts as an albuminous adhesive and attaches the cells to the glass slide upon which they are spread. One should attempt to distribute the cell.mass somewhat evenly over the surface of the clean glass slide, although great care in achieving thinness is not essential. It is more important to make the smear quickly and then plunge it before it has had a chance to dry into the fixing solution. This solution consists of equal parts of 95 per cent alcohol and ether. In

it the slides may be stored for days without danger of deterioration. It is well to place a paper clip on each slide to prevent rubbing against one another and thus prevent marring of the smear. The paper clip is also useful in attaching small piece of paper with essential data, such as the name and date, to the slide.

It is well to remember when securing material from the vaginal fornix that any procedure which effects a dilution, such as bleeding, douching, vaginal examination or coitus, should be compensated for by making multiple rather than single smears. Of course a few hours' delay, if practicable, would be even more efficacious thus allowing a reaccumulation of cellular material.

Staining of the smears is a very important matter, and one to which a great deal of attention has been given. Perhaps unfortunately, what we have to say about diagnostic possibilities of the vaginal smear can only pertain to the properly stained one. Because of the mucus present in the material, translucency can only be obtained by use of alcoholic stains. Watery solutions produce clogging and obscure cellular detail. A good nuclear stain is essential, particularly for cancer diagnosis. In addition, the cytoplasm and its inclusions must be allowed to react to acid as well as alkaline dyes. These staining requirements though not complex are definite and must be met if success is to be realized. Several good stains, already compounded and in solution, are available on the market. As the staining is of greatest importance and should be uniform, it is well to carry out the process, staining several slides at a time in small metal racks. This also serves to cut down the total time consumed and will serve to remove one of the chief technical obstacles to the method. In the ordinary office a nurse attendant can easily be trained to carry out the procedures. If later one trained to miscroscopic diagnosis can afford to spend some time in scrutiny of the slides, both the physician and the patient will benefit.

Study of the stained Smear Preparations

This is a time-consuming process and usually requires a trained cytologist with some experience for ultimate diagnosis, although much can be done by self-training on the part of any interested physician. The average slide should be accorded at least five minutes' study, and some will require twenty or more. Thoroughness is the keynote of success. The work, therefore, should be done by those having had training and who may be given adequate time for the purpose. This will usually mean a pathologist with a central laboratory to which preparations may be sent for staining and study. In all probability it will only be exceptionally that the gynecologist will have the training and the time to stain and study the smears.

A detailed description of the various types of cells to be found under changing circumstances together with their significance

cannot be entered into here. To learn to recognize them is a matter of training at the microscope. However, some indication can be given briefly, referring those seriously interested to the literature and the atlas already available.

Normal Menstrual Cycles

Preovulatory phase: the large cells are essentially flat and discrete, do not tend to agglutinate. The individual cell has a cytoplasm which has an affinity for the acidophilic stain and contains toward the end of the phase, small round granules which we think from their size and number may be an expression of the degree of estrin influence. The nucleus is relatively small and is basophilic.

Postovulatory phase: the cytoplasm tends to become basophilic; the inclusion granules disappear. The edges of the cell tend to crinkle and the individual cells adhere to one another as though sticky. The nuclei are generally paler in their reaction to the basophilic stains and are much increased in size.

These changes are marked and with a series of vaginal smears taken at different stages in the cycle, at four or five day intervals or weekly, serve to give a reliable record of ovarian function. Combined with basal body temperature records the two sources of data form the most reliable basis for the study of utero-ovarian relationships.

The post-menstrual phase, as also the premenstrual and menstrual, have definite cellular responses which are recognizable and may be of importance in any complete study of individual cases.

Anovulatory Cycles

These cannot be discerned except by following a series of smears at weekly intervals over the whole month or a succession of months. Because the woman of normal intelligence can easily be taught to make smears from her own vagina, fix them and bring them to the laboratory, such a study becomes an easy and relatively inexpensive method of following the fundamental reproductive processes of an individual.

The first anovultary cycle is expressed in the vaginal smear by a persistence of the various criteria which have been outlined for the preovulatory phase. That is, the cytoplasm of the cell remains acidophilic beyond the time for normal ovulation; *viz.*, fourteen days before menstruation, and the cells gradually become pyknotic as menstruation approaches. There is little or no tendency for the cytoplasm to become basophilic and the agglutinative tendency of the ovulatory cycle does not appear.

With the second anovulatory cycle the cytoplasm becomes more acidophilic, that is it takes the eosin or fuchsin dye (red) in greater degree. More of the brown inclusion bodies may be noted and the nucleus remains relatively small and densely basophilic.

When three anovulatory cycles occur successively, the vaginal smear approaches what one observes in association with cystic glandular hyperplasia of the endometrium. It is an expression of unopposed estrin influence, without much shedding of the endometrium and without adequate progestin or corpus luteum influence. In the vaginal smear this is represented by an abnormal affinity toward acidophilic strains, smaller individual cells of discrete nature, many of which show keratinization, and in addition the cytoplasm includes large brown, round bodies. The nucleus remains small and densely basophilic.

Cystic Glandular Hyperplasia or Hyperestrinism

The description just given for the third anovulatory cycle is apt in depicting what may be observed in the vaginal smear under these circumstances. Hyperkeratinization of discrete cells may be a fair summary of the findings. In our experience the degree of acidophilic response of the cells in hyperestrin states is only approached by the cells in trichomonas vaginitis infections. Many patients checked by both vaginal smears and curettage biopsy have taught us that the diagnosis is as clear in the interpretation of the vaginal smear as upon curettage—an important application of the procedure to office gynecology.

Amenorrhea

In primary, as in secondary amenorrhea, the cellular response as reflected in the vaginal smear, is one of degree. In the individual who has a marked pituitary or ovarian lack the smear may more or less nearly approach that of the postmenopausal or senile woman.

In scanning smears from the vaginæ of such indviduals, one will observe many small basophilic cells with nuclei disproportionately large. The individual cells have a round or oval appearance and have a uniformly homogenous cytoplasm. The nuclei show a normal chromatin content, but relatively few nucleoli. One can judge of the degree of ovarian or pituitary suppression by a comparison between the larger or more mature cells and those of a small, atrophic appearance.

In following various attempts at therapeutic correction, the vaginal smear is an indispensable index as to the efficacy of such treatment. For with stimulation of the gonads by the use of gonadotropins—when it rarely occurs—one can observe a response in the appearance of the more mature forms of cells in the vaginal smears. Or if one chooses to use estrogens, one can quickly observe the appearance of cells of such a cell pattern as we have described under preovulatory phase of the normal cycle; that is, large, well formed, flat, discrete, acidophilic cells. In this way the effects of therapy can be evaluated. In addition, as most often happens, the persistence of the cells characteristic of preovulatory phase, without the advent of basophilic change plus crenation and agglutination

of the cells, serves as a caution to the therapeutist that he has fallen short of the objective—*viz.*, normal ovulation, and thus may be used as an indication and guide for progestin therapy in combination with the use of estrins.

Pregnancy

In our experience the vaginal smear is of little or no assistance in the diagnosis of early pregnancy. However, pregnancy after the second or third months shows a profound change in the character of the cells which are observed in the vaginal smear. The individual cells are about one-half the size of those of the normal menstrual cycle and tend to be more basophilic. They undergo a marked change in form also, in that they are clumped and are boat-shaped as to cellular outlines and as to nucleus.

Vaginitis

The various forms of vaginitis, that occurring during the reproductive period of life and that seen in the postmenopausal period, are characterized by definite findings in the vaginal smear.

In trichomonas infections one may see the stained trichomanads and in addition there is a most advanced and marked degree of keratinization to be observed in the cells of the vaginal smear. Because of the keratinization one should be careful to differentiate between hyperestrin keratinization and that due to the trichonomas flagellate. The latter produces clumped, often anuclear cells which take the acid stains excessively. Having observed these forms one should at once look for the small basophilic trichomonads. Finding them clinches the diagnosis. In hyperestrin states, as has been said, the cells are large, discrete, acidophilic and contain numerous brown, round inclusion bodies in the cytoplasm.

In monilia vaginitis one sees the branched yeast forms surrounded by large basophilic epithelial cells. The picture is in marked contrast to either of the foregoing clinical entities. Inasmuch as the therapy of these infestations is quite different, these smear pictures lead toward a specific therapeutic approach which cannot be equalled except by means of extensive and expensive laboratory technics.

Menopause

The menopause is characterized by declining pituitary and gonadal function. This is reflected in the cells of the vaginal smear by the presence and gradual increase in the numbers of small round or oval, increasingly basophilic cells of the atrophic type, in many ways analogous to those in the smears of amenorrheic individuals. One can follow the gradual subsidence of ovarian function by occasional smears. The cellular picture is a most graphic and reliable index of ovarian function. Our studies in hundreds of women have taught us that contrary to common thought the decline in ovarian function in normal woman begins about the age of 35 and continues

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gradually until the age of 52 or 53. Thus the physiological meno pause is seen to be a much longer period of time than has been usually thought, almost twenty years being the usual course.

When emotional disturbances intervene, as they frequently do in our modern urban-dwelling women, the vaginal smear forms a most useful means of directing estrin therapy. When estrins have been given to a point where the preovulatory type of cell has replaced the small atrophic cell forms, one can be sure that adequate therapeutic intervention has been realized. Estrin medication beyond this point is seldom indicated, unless perhaps it might be in the control of migraine, although this indication is dubious. Thus the estimation of cellular response as based upon the veginal smear content may be a most useful guide toward the treatment of the menopause syndrome.

Cancer of the Female Genital Tract

Carcinomatous lesions of the endometrium endocervical and portial epithelium are characterized by exfoliative tendencies even in the earliest lesions. As the cancer cells show typical abnormalities in their nuclei, scrutiny of the vaginal smear becomes the best means we now have for the early diagnosis of cancer in the female generative tract. Because even the intraepithelial lesions which cannot be detected by the eye or by the Schiller test exfoliate cells, the routine examination of vaginal smears becomes an obligate 'duty of every physician until such time as a better method has been attained.

The recognition of the characteristics of malignant cells, whether of cervical or endometrial origin, is a matter requiring experience. The pathologists look at tissue preparations obtained by local biopsy and come to a conclusion by observing individual cells, but also by the relationships of other cells, invasion, mitoses, etc. The vaginal smear diagnosis is based upon the evaluation of individual cells, sometimes in clumps, but more often scattered individually over the surface of a smear preparation. Because of the inherent difficulties, which are real but often over-estimated, we have always taken the attitude that the smear diagnosis should be seconded by a positive biopsy preparation. Most often this is eventually possible. But nothing in cancer diagnosis is more illuminating—and we may say disillusioning—than the frequently necessary repeated attempts at biopsy demonstration in the presence of continuously positive smear preparations. The biopsy is necessarily selective, whereas the vaginal smear is diffuse and all-inclusive. The lattar requires careful search as compared to the former. However, because early lesions may be found by the smear studies, it has an advantage beyond that of biopsy technic.

The characteristics of cervical cancer as reflected in cell preparations—smears—pertains principally to the nucleus. Cancer

is a disease of the nucleus and visually may be detected there in the changes in size and form and in the chromatin organization of that part of the cell. As has been said. experience is necessary in attaining skill in evaluating these variations. But this should not be over-emphasized, because many resident house staff physicians under our system of training have attained proficiency. This should mean that any pathologist, without a mental block and possessed of a real desire to learn, can achieve the requisite judgment.

Endometrial carcinoma is more difficult because the cells are smaller and are nearly always shed in clumps. They stain densely and hence require a good preparation for recognition. But here, too, experience leads toward success, and we have repeatedly diagnosed lesions so early that repeated curettage failed to substantiate a smear diagnosis, which was subsequently proved correct.

It should be emphasized that the smear preparation and its evaluation should be backed up by biopsy findings in the corroborative sense before radical therapeutic procedures are resorted to However, experience has shown that sometimes the biopsy fails repeatedly. In these instances, when the smears are repeatedly positive over a period of time, it may be well to apply the appropriate surgical approach. In doing so, in carefully selected cases we have been rewarded, not only in curing a patient in the most susceptible phase of the disease, but have learned in addition that cellular smear diagnosis may occasionally be, in good hands, more reliable than biopsy technics.

Training Necessary for Vaginal Smear Diagnosis

Any interested physician with a good microscope and a laboratory to adequately stain routine smears can achieve some of the most important features as we have outlined them. He should be able to recognize all phases up to and including the menopausal characteristics. Many will in addition at least attain the proficiency necessary to make them suspicious of malignancy.

However, the chief benefits from scrutiny of vaginal smears will come only when routine smears are taken, not only upon the occasions when a woman presents herself voluntarily, but when such presentations are dictated by a public health policy operating in an enlightened community. If ever we give our women the followup care which the dental profession has established, then we will be approaching what our present knowledge is capable of affording in gynecological matters. Such smears usually should be processed through a central laboratory and submitted to thorough scrutiny. General pathologists may easily be trained to this form of service, though they have been somewhat resistive because they have lacked confidence in the method on one hand, and on the other it takes longer to search a vaginal smear adequately than it does to look at a tissue biopsy. Histologists are more easily trained because they are usually more amenable to the scrutiny of individual cells, upon which the vaginal smear as well as the blood smear is based. In teaching hospitals where resident staff physicians are rotated in their course of training through the pathological laboratory one can because of his proximity to the patient as well as his association with the laboratory, be rapidly convinced and taught. Physicians having this type of training will ultimately prove the bulwark against many gynecological diseases and in their practice do much to ameliorate many of the diseases peculiar to women.

This necessarily brief outline is merely an indication of the possibilities of the vaginal smear technic in gynecological diagnosis.

(Rocky Mountain Medical Journal, May 1947.)

MEDICAL ASPECTS OF MALIGNANT LESIONS OF THE ANUS, RECTUM AND COLON

E. G. Wakefield, M. D., *Division of Medicine*: Diagnoses of malignant lesions of the anus, rectum and colon are made by the proctologist, the roentgenologist or the general surgeon at the time of surgical exploration. These diagnoses are confirmed by study of the tissue by the pathologist. A diagnosis of a malignant lesion should not be recorded on the history without a pathologic report which would substantiate such a diagnosis.

The treatment of uncomplicated malignant processes of the anus, rectum and colon is prescribed by the surgeon. In a few cases the treatment is then executed by the proctologist, but generally, however, by the surgeon. As an adjunct to treatment or solely as a palliative measure, irradiation with radium or roentgen rays may be emplicated. Malignant lesions of the anus, rectum and colon may be employed by the existence of other diseases in various regions or systems of the body, or they may have complications as results of themselves—that is, extension or metastasis.

The complicating diseases which may prove hazardous to the patient while the surgeon is carrying out his procedures commonly are the results of acute or chronic infections of the respiratory system, disease of the heart or kidneys, diabetes, hyperthyroidism, gout or any other diseases characterized by chronicity, with a tendency to relapse or recur after operation. A great number of patients in the age groups in which malignant lesions of the anus, rectum and colon occur have hearts, blood vessels or kidneys which are not capable of full functional activities. Generally, however, no special preoperative preparation is made for these patients unless there is some objective manifestation of decreased functional activity in these organs. If there is evidence of decreased functional activity in these organs, it is well to observe the patient long enough to be able to evaluate the limitations of function, and

perhaps to administer appropriate amounts of digitalis, insulin, antibiotic agents or to carry out other appropriate supportive measures such as the intravenous administration of fluids, if dehydration or hyperazotemia is present. Phlebitis or thrombophlebitis is a common occurrence. In such cases rest and bandaging and elevation of the part until the acute phase of the process has subsided are indicated.

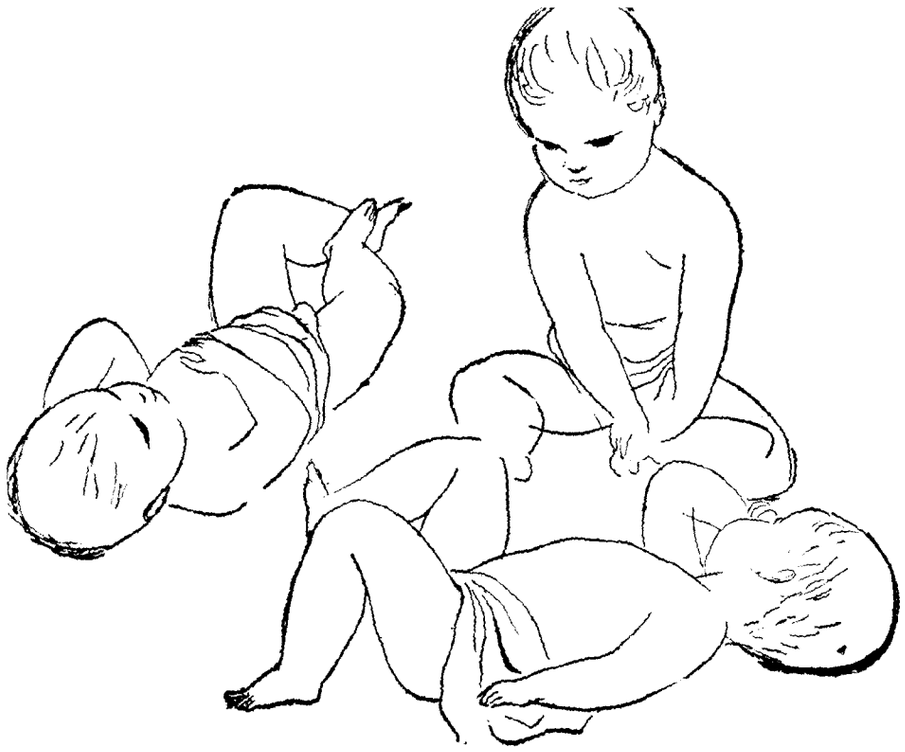
The complication of the malignant process itself which is of prime importance is metastasis, and in by far the greater number of cases, metastasis from malignant lesions of the rectum and colon occurs in the liver. It should always be kept in mind, however, that an enlarged liver does not necessarily indicate that metastasis has occurred. If there are no evidences of metastasis other than a slightly enlarged liver, it is generally well to proceed with surgical exploration.

In lesions of the colon, and especially of the right half of the colon, which have been present for a long time without symptoms, a constant loss of blood may be followed by rather severe hypochromic anemia. Such a type of anemia is related to the chronic loss of blood, rather than to any sort of toxin produced in the colon. Anemia of this type is amenable to blood supplied by transfusion.

All patients before operation are hospitalized for a few days to a week for preparation for surgical operation. This preparation consists in the administration of a saline laxative agent, such as a saturated solution of sodium acid phosphate, whih is administered once or twice a day. It is not necessary to administer enough of the saline laxative to make the patient too uncomfortable. The whole aim of the saline laxative is to produce a liquid or semiliquid stool which can be readily removed by colonic irrigation. Colonic irrigation is carried out twice a day during the preoperative period. It is usually continued until the return flow is clear. In the hospital these patients receive a high carbohydrate diet. This diet is not adequate and should not be prolonged if for any reason surgical treatment is postponed.

In cases in which the malignant process itself has produced local complications, such as small degrees of intestinal obstruction lowgrade perforations, very little change is made in the routine preparation of the patient. Where the malignant lesion is so situated, or is of a configuration such as to produce intestinal obstruction, then alterations in preparation of the patient for surgical operation are necessary. In such cases, nasal suction is instituted and hot abdominal stupes are applied. In some cases the administration of a saline laxative agent through the nasal tube will help to relieve the obstruction. Of course, the tube should be clamped after introduction of the laxative. The colon is again irrigated twice a day. Sometimes, beneficial results may be obtained by

carrying out the irrigation while the patient is not in knee-chest position. It is essential to administer fluids intravenously every day that the nasal suction tube is in operation. Every attempt should be made to replace, by intravenous administration, the volume of fluids that is removed through the nasal tube. It must be realized, however, that the intravenous administration of fluids will not replace all the electrolytes that are lost through nasal suction. Prolonged nasal suction is undesirable, and as soon as it is clear that the intestinal obstruction is not going to be relieved by the so-called conservative methods, surgical treatment should be resorted to immediately. The surgeon is not pleased by having to operate on a patient who has obstruction of the rectum or colon which has not been relieved by medical means, because operations in such cases usually are only palliative, and although they may be livesaving, the patient in the end is subjected to an extra operation.



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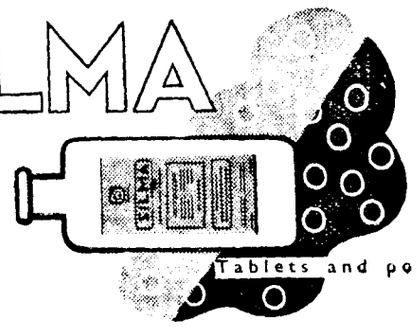

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Medical Notes & News.

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PRESS NOTE.

Intimation has been received from the Registrar, General Council of Medical Education and Registration of the United Kingdom, to the effect that the Council has recognised for the time being the M.B. B.S. degree granted by the Andhra University with effect from the 11th January, 1947, and the holders thereof shall be entitled to be registered accordingly in the Colonial List of the British Medical Register.

Regd. No. M. 2853.

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ANTIMALARIAL DRUGS

J. C. PATEL *

In recent years (during World War 1939-1945) a large amount of research work has been done and much has been learned concerning the use of antimalarial drugs. The significant developments that have occurred will be discussed in this review.

QUININE AND OTHER CINCHONA ALKALOIDS.

Cinchona alkaloids have been in use in the treatment of malaria for over 300 years and quinine for 100 years. Nine-tenths of the world's supply of cinchona came from Java where the climate favoured the growth of cinchona trees. Even though there were a few cinchona plantations in Ceylon, India and South America, the production and quality were poor.

Pharmacology.—As a result of several years experience with sulphonomide drugs, the world has now become very conscious of plasma levels. These estimations have been done after administration of quinine. The plasma concentration of quinine reaches a peak within four hours of oral administration, but falls rapidly. The rates of absorption and excretion of quinidine and cinchonidine have been found to be similar to those of quinine except that those of cinchonidine were slower and less complete. To be effective quinine has to be administered frequently and continuously. After a routine administration of 30 grs. per day divided in three doses the plasma concentration reaches from 0.3 to 1.0 mg. per 100 c.c. The effective level varies with different hosts and species and strains of parasites; a level of 0.3-0.5 mg. is effective except for *P. falciparum* which requires a level of 1.0 mg. per 100 c.c. The effective level of other alkaloids is of a similar order except that of cinchonine which is effective at a lower level (Sinton, 1929).

Clinical Experience.—The Madras Cinchona Committee in 1867-1868 first reported that the action of the four principal cinchona alkaloids quinine, quinidine, cinchonidine and cinchonine was equal on malaria. These observations were confirmed by several observers not only in India but also in other countries. Field experiments (Green 1945) also showed that totaquine mixture consisting of about 70 per cent total crystaline alkaloids of which not less than one fifth is quinine, was as effective as quinine alone in approximately the same dose. The only disadvantage is that the by-effects (nausea, vomiting and cinchonism) were more frequent.

* From the Department of Medicine, King Edward Memorial Hospital, Bombay.

These by-effects were ascribed to an amorphous alkaloid in the mixture. The totaquine mixture has no advantage over quinine alone in preventing relapses; neither would act as true casual prophylactic. By casual prophylactic is meant destroying the parasite before it enters the red blood cells To achieve it a drug must kill either the sporozoites or the exoerythrocytic (e.e.) forms As the drug is absorbed quickly no higher initial dose is necessary as with other drugs like mepacrine or the sulphonamides. The dosage recommended is 30 grains in three divided doses for seven or eight days.

Mode of Action.—Recent literature contains few additional data on the clinical effects of quinine, most studies being concerned with an evaluation of synthetic drugs as compared with quinine. Quinine does not destroy sporozoites or gametes of *P. falciparum*. The mode of action upon schizonts is still under debate.

As a suppressive drug quinine was used extensively in World War I and later. It was believed to be effective. Any failure was ascribed to an improper and irregular administration of the drug. However, some doubted its effectiveness. Fairley (1945) and Findlay and Stevenson (1944) used quinine in a dosage of five to ten grains per day in the army, in controlled experiments and it proved a failure as a suppressant. This probably occurred because of its rapid absorption and excretion, the plasma concentration not remaining high for a sufficiently long time to have action on the parasites. None of the other cinchona alkaloids could be more effective because of the same reason, As a suppressant drug quinine has given way to one of the synthetic drugs, mepacrine or paludrine. The value of quinine and other cinchona crystalline alkaloids in anti-malaria therapy is equal and a mixture of these alkaloids can be used as a completely efficient substitute for the single alkaloid quinine.

MEPACRINE

Mepacrine was in use for more than 10 years at the time (1942) Java was lost with its quinine supplies. This drug had definitely been considered an effective antimalarial and was even believed to have some advantages over quinine in therapy, and certainly superior in suppression of malaria. Quinine had been successfully used for three hundred years and was no less effective than mepacrine and hence quinine was still considered to be the drug of choice. Another reason for this preference was a political and economic one. Mepacrine as Atebrine was manufactured only in Germany and the exact method of manufacture was not disclosed. With the loss of quinine from Java more attention was paid to mepacrine and considerable amount of research was done during war time. Plans for large scale production were laid. Various names were given to it in different countries. It was called mepacrine hydrochloride (B. P.), quinacrine hydrochloride (U.S.P.), Acriquine

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(U. S. S. R.), Crindora (Italy), Haffkinine Acriquine (Bombay). Most of the work till the beginning of the war was done with the German manufactured drug As the method of manufacture was not disclosed there used to be doubts about identifying the drug manufactured in other countries with the German drug. Chemical, pharmacological and clinical investigations sponsored by National Research Council (U.S.A.) and Medical Research Council (England) established the identity of the American and English products and numerous investigators showed that they were no more toxic than the German product.

Pharmacology.—Methods of accurately estimating mepacrine in blood plasma, urine and tissues were devised, and accurate methods were developed. This was important as the action of a drug is dependent on its concentration in the blood plasma and tissues. Shannon, *et al* (1944) found that when mepacrine was given either by mouth or by intramuscular injection, a large proportion, 90 per cent was fixed in the tissues, about 3 per cent was excreted in the urine and about 6 per cent in the fæces, in the first twenty-four hours. When the drug was stopped the excretion rate fell off rapidly but traces were found in the urine for many weeks. On the ordinary daily dosage of the earlier therapeutic regimes, the maximum plasma level is not attained for several days, but once the balance between the intake on the one hand and the rate of excretion and degradation on the other has been achieved, a fairly uniform plasma level may be expected. In persons taking a regular daily dose, the general rule is that 40 per cent of the final level is reached at the end of the first day and 40 per cent of the deficit is made up each day subsequently, so that 90 per cent of the peak level is attained by the end of the fourth day. If however the dosage on the first day is doubled, this plasma level is attained at the end of the second day and if it is trebled, this near peak is attained on the first day and the peak level for that particular dosage can be maintained subsequently by the ordinary daily dosage. Conversely, when the drug is discontinued the plasma level falls at the rate of about 20 per cent daily for several days but traces of mepacrine are still present even after eight weeks. If 0.4 gm. per week is used in suitable divided doses a peak level of between 8 and 15 microgrammes is obtained about the end of fourth and fifth week. But a level of 15 to 30 microgrammes with a mean above 20, is reached with the same time if the dose is increased to 0.6 gm. per week given in six doses. As it takes a longer time to reach an effective level, the prophylactic treatment should be started two weeks before the date of entering an endemic zone and if the time is short dosage should be increased and a single loading dose of 0.6 gm. should be given before commencing the ordinary regime (*Army Medl. Bull.* 1945.)

The behaviour of mepacrine is thus in sharp contrast to that of quinine which appears very early in the blood in relatively higher concentration, reaches its peak concentration in about four hours and falls far below the therapeutic level by the end of twenty-four hours.

The plasma concentration of mepacrine necessary to effect a clinical cure in malaria, varies both with the host and with the strain of parasite but it is generally believed that a minimum level of 30 microgrammes is required. During suppression therapy an overt malaria does not occur if the plasma level is above 12 microgrammes.

Toxic Effects.—Mepacrine may cause (*a*) gastro-intestinal disturbances—abdominal pain, vomiting and diarrhœa ; (*b*) symptoms related to the central nervous system such as cephalagia, mental depression, delirium, psychosis and convulsions ; (*c*) collapse and death. However the incidence of these symptoms is low. It varies with a number of factors. It is higher (1) in children (2) in psychopaths, (3) in those in whom the drug is given by injection. (4) when given with other drugs particularly plasmochin, (5) in the poorly nourished, and (6) when the dosage was high initially. These toxic effects can be obviated by such simple means as taking sodium bicarbonate or glucose at the same time. Besides most of them for example, the gastro-intestinal disturbances and the mild psychosis that sometimes follow the early doses—frequently do not occur later during the course when some tolerance for the drug has been established. They are therefore not an indication for discontinuing the drug altogether, not even, except in rare instances, for modifying the dosage. Mægraith, *et al.* (1945 a, b and c) have shown that mepacrine in the usual dosage for treatment as well as for suppressive therapy does not cause any damage to the liver or kidney and it has no deleterious hæmatological effect on blood cells even when the drug is continued for 12 months (Mægraith *et al*, 1945. c.)

Dosage.—The recommended and used dose of the German drug up to the last war was administered in doses of 0.1 gm. three times a day, for 5 days, for a total of 1.5 gm. From the newer knowledge of the absorption and excretion and the level of plasma concentration and from also the clinical experience gained during the war (1939-1945) in army personnel, it becomes obvious that the usual recommended dosage was insufficient. In order to reach the high level required for adequate concentration, a high initial dosage was necessary. This applied whether the drug was given by mouth or parenterally. Different doses have been recommended but most often 0.8 to 1.0 gm. is administered in the first twenty-four hours. The United States Army (1944) prescribed 0.2 gm. of mepacrine immediately and then every six hours, night and day, during the first twenty-four hours to a total of 1.0 gm. and 0.1 gm. three times a day for a further six days to a total of 2.8 gm. in all.

For the parenteral administration the intra-muscular route is preferred to the intravenous. as it is safer and has no disadvantages. If it is given intravenously it should be given very slowly. If the parenteral method is indicated, as in the unconscious patient. two injections of 0.2 gm. of mepacrine in 5 c.c. of distilled water are given into the gluteal region one on each side at an interval of six hours. Administration by the oral route should be begun as early as possible but if for any reason this is delayed beyond six to eight hours, another intramuscular injection should be given and repeated every eight hours until oral therapy can be instituted. The total dosage both by the oral and parenteral route in the first twenty-four hours should be 1.0 gm.

Action.—In the usual dosage mepacrine destroys exœrythrocytic forms as well as asexual blood parasites in malignant tertian parasites. In *P. vivax* mepacrine has action on asexual blood parasites but not on the tissue stage (exœrythrocytic forms). Hence the tendency of B.T. infection to relapse repeatedly despite the prolonged anti-malarial treatment with mepacrine.

For suppressive therapy a daily dosage of 0.1 gm. is given. This dosage should be started not less than two weeks before the subject enters a malarious area. If the entry is earlier higher initial dosage is necessary to bring up the level of plasma concentration. On this dosage (0.6 to 0.7 gm mepacrine weekly) malaria suppression was adequate and, provided the drug was continued for the prescribed period, cure invariably resulted with *P. falciparum*. But in *P. vivax* infection a similar mepacrine regimen was effective in preventing avert attacks of benign tertian malaria only while the drug was taken, as they occurred as soon as the drug was stopped. On this suppressive therapy (0.6 to 0.7 gm. weekly) no attacks of malaria occurred (Fairley 1945) even when non-immune persons were exposed to infective bites in a hyper-endemic area of malaria in the jungle. Even under all the stresses and strains of hard physical work, prolonged marches, exposure to extreme cold, and flying at high altitudes no malarial attacks occurred. As a result of this prophylaxis, gametocytes would never appear in the blood and there would be no malaria carriers. There would be no deaths due to cerebral malaria and no attacks of blackwater fever.

Mepacrine is definitely superior to quinine both as a curative and suppressive agent but has the disadvantage of colouring the skin and a few toxic effects. However, they are not as frequent as might be thought.

PALUDRINE

The loss of supplies of quinine as a result of Japanese occupation of countries producing quinine in 1942 induced the chemists and biologists to engage in a search for a new antimalarial drug. The quest for new synthetic antimalarials was mainly centered round derivatives of quinoline and acridine, the basic structures of

pamaquine and mepacrine, respectively But paludrine has been developed on entirely different chemical lines. Curd, Davey and Rose (1945) in England started their search by investigating the activity of pyramidine and its derivatives in bird malaria. Pyramidine was chosen because of its presence in nucleoprotein and associated enzyme systems and because of its proved value as a component in certain sulpha drugs particularly sulphadiazine which were known to possess antimalarial activity. It was found that antimalarial activity was enhanced by introduction of a guanidine group in pyramidine nuclei. The first compound produced was active in human malaria but had unpleasant side effects. Finally, two highly potent antimalarial drugs were produced, *viz.*, 4430 and 4888. These drugs were both very active against the blood forms of P. gallinacum and were also found to affect the exœrythrocytic forms of the parasites. This activity against exœrythrocytic forms of avain malaria is practically unique amongst antimalarial drugs and in this respect 4888 was found to be more active than 4430. 4430 was originally given the name "Paludrine." As 4888 has been found to be a highly efficient antimalarial drug in human cases, the manfacturers (I.C.I. Ltd.) have transferred the name "Paludrine" to 4888.

Composition.—"Paludrine" is known chemically as N_1P-chlorophenyl-N_5 isopropyl-biguanidine. Paludrine is a base which forms salts such as the hydrochloride and acetate. The hydrochloride is an odourless, bitter, white crystalline powder having a melting point of 240°C. It is a stable salt which dissolves slowly in water giving a solution that may be boiled without decomposition.

Pharmacology.—Paludrine is absorbed rapidly and almost completely from the gastro-intestinal tract. It can be estimated in blood by a colorimetric method described by Spinks and Tottey (1945) and by King (1946). It has been shown that peak levels are reached within three hours of administration. Fall in concentration is rapid, although sufficient may remain after twelve hours to cause a build-up if the drug is taken twice daily. This reaches its maximum after four or six doses (Mægraith, Adams *et al* 1946). Paludrine is present in cells in four times the concentration in the blood plasma. The drug is rapidly excreted, more rapidly than mepacrine. Even after a dose of 500 mg. twice daily, the blood level falls below the level of estimation within one week from the cessation of the dosage and the drug cannot be detected in the urine after nine days. It is not surprising, therefore, that no ill-effects have been reported following long continued dosage for prophylactic effect. Despite the rapid excretion of Paludrine its potency is so great that frequent dosage is unnecessary.

Toxic Effects.—In animal experiments Paludrine has produced no adverse effects on blood pressure, respiration or intestinal movement. There are no toxic effects in the usual therapeutic dosage adopted, *i.e.*, 300 mg. for 10 to 21 days. The toxic effects of the drug

have been observed in experiments at Cairns (Australia) with high dosage as 1.0 gramme daily. They may be described as gastro-intestinal, urinary and hæmatological.

(*a*) Gastrointestinal effects: Vomiting commonly occurs in patients with overt malaria or when the first total daily dose 1.0 gramme is given as a single dose or in 5 divided doses of 200 mg. each. However if the treatment was begun with 100 mg. three times a day on the first day vomiting was no more frequent than with other antimalarial remedies, such as quinine or mepacrine given to patients with overt malaria. Abdominal pain, vomiting and some diarrhœa for 12 hours developed in two patients. Mægraith *et al* (1946) noted abdominal discomfort and nausea in some patients when a dosage of 500 mg or more was given.

(*b*) Urinary changes: In patients who were administered high dosage of 1.0 gramme daily for 14 days there was microscopic hæmaturia, in some frank hæmaturia, albuminuria and granular casts and, in one, blood casts in his urine. But in none, there seemed to be any real damage to the kidney. No case developed symptoms suggesting nephritis. Both the urinary and gastrointestinal toxic symptoms were, in general, of minor significance. They occasioned no anxiety, were related to initial high dosage of paludrine in patients sick with overt malaria and were relieved by diminishing the dose.

(*c*) Paludrine tends to produce leucopenia but not agranulocytosis, and a slight increase of myeloycytes.

(*d*) Parekh (1947) observed dermatosis in two out of a series of 48 cases.

N. H. Fairley (1946) has given an excellent account of his experience with Paludrine in "a series of experiments performed to determine the antimalarial activity of Paludrine in volunteers infected with New Guinea strain of *P. vivax* and *P. falciparum*." He discusses the drug under the following headings:—

1. *Supression and Causal Prophylaxis*:

Volunteers were subjected to a large number of infective bites (120 *P. vivax* and *P. falciparum*) over a period of 62 days during which they were exposed to fatigue and cold. While taking paludrine (100 mg. daily) no parasites were demonstrated microscopically in the blood and there were no minor symptoms of malaria sometimes encountered with other drugs and no toxic effects whatever. When the drug was withdrawn overt vivax malaria developed in from 24 to 33 days but no falciparum fever was met with. Carefully planned experiments have shown that it is the primary wave of the pre-erythrocytic forms that is inhibited in both vivax and falciparum infections contrary to what obtains with the other drugs where the action is mainly schizonticidal. In falciparum infection the lethal effect is complete and the cure is radical while

in vivax infections some of the pre erythrocytic or early e.e. forms survive and commence schizogomy when the drug is stopped.

These experiments also indicated that 50 mgs. of paludrine daily or 100 mgs. twice a week would constitute an effective dosage regimen for non-immunes in highly malarious areas

2. *Therapeutic Action :*

Paludrine is a powerful schizonticide both in vivax and falciparum infections interfering with nuclear division of early schizonts. Given daily in doses of 300 mgs. for 10 days falciparum malaria was cured in 104 out of 105 individuals The results in vivax infections though good are not consistently so. It is considered that 300 mgs. daily for 21 days would serve as an overall course, radically curing falciparum malaria, clinically curing vivax malaria in most cases permanently, and preventing infection of mosquitoes for at least a period of 33 days.

3. *Drug Control of Malaria in Indigenous Native Population :*

The low toxicity of paludrine and its effective action on the parasite give it an important place in any plan for the control and eradication of malaria in infested areas. The experiments mentioned above were made with non-immunes and it was proved that effective control could be exercised. What the results in native populations with premunity will be like have still to be adequately worked out. Komp and Clark (1936-1937) found that eliminating premunity by producing early radical cure resulted in the local population becoming highly susceptible to an epidemic and reacting very severely to re-infection while adjacent villages escaped lightly.

4. *The Action of Paludrine on Gametocytes :*

Paludrine has no action on gametocytes circulating in the blood. If a gametocyte carrier taking paludrine is bitten by a mosquito, the quantity of the drug present in blood of the carrier is sufficient to prevent the development of cycle in the stomach of the mosquito. If the drug is given to the patient in the early stages development of gametocytes may be prevented. Gametocytes of P. vivax are killed during the course of ten days of treatment of clinical attack but not those of P. falciparum.

Maegraith *et al.* (1946) have tried the drug in more than 157 cases of malaria of Mediterranean, Indian and Burman origin. They have come to similar conclusions as workers at Cairns. They have found it effective in varying doses from 10 mg. to 750 mg. and of 50 to 600 mg. twice daily for 14 days in the treatment of benign and malignant tertian malaria, respectively. They found that the administration of single doses of 50, 100, 200, 300 and 400 mg. produced clinical cure of relapsing and delayed primary cases of benign tertian malaria. The same effect can be produced by 400 mg. of mepacrine. They did not find the drug toxic except for occasional nausea. They considered the absence of a colour an advantage.

When ordering please mention *Medico-Surgical Suggestions.*

In the treatment of malaria the following dosage has been recommended :—

Malignant tertian and quartan malaria : 0.1 gm. three times a day for 10 days or 0.1 gm. twice a day for 14 days will produce a radical cure.

Benign tertian malaria: For an acute attack the above dosage will produce a clinical cure. Paludrine will not prevent relapse. But if the drug is given in the dosage of 0.1 gm. twice weekly, evenly spread out, for six months the chances of relapse are far less than with other antimalarials.

Paludrine has not been used by the parenteral route because the drug is rapidly absorbed. In cerbral malaria 0.1 gm. has been given intravenously without any toxic effects.

CHLOROQUINE.

From among the 14,000 substances, both natural and synthetic, which were examined in an intensive search for antimalarial drugs in America, S.N. 7618 was found to have antimalarial activity and given the name Chloroquine. It has been the subject of two reports in recent American Medical literature. Chloroquine has been compared to mepacrine hydrochloride the synthetic drug, as regards its various properties.

Absorption, excretion, tissue distribution and degradation.—Absorption of chloroquine from the gastrointestinal tract is complete and somewhat more rapid than mepacrine. It is present in higher concentration than mepacrine in the blood on any given dosage schedule. Deposition of chloroquine in the various tissues is similar to that of mepacrine. S.N. 7618 like mepacrine is metabolised in the body, only a small part of the drug administered being found in the excreta. Ten to twenty per cent is excreted unchanged in the urine and it can be increased by acidification of the urine and decreased by alkalization. The localisation of S.N. 7618 in the organs with slow rate of excretion and degradation necessitates the administration of a large initial dose of the drug for attaining the high concentration in the plasma which is required immediately and which is to be maintained. The concentration in the body fluids slowly falls after the drug is discontinued and it falls by 60 per cent in a week. The minimal plasma concentration of chloroquine that is required for terminating an acute attack is in the range of 10 microgrammes per litre. In experimental animals S.N. 7618 behaves in the same manner as mepacrine both in short and long term experiments. S.N. 7618 is slightly less toxic than mepacrine.

Antimalarial Activity.— Chloroquine is more active than mepacrine in all the avian malarias in which it has been tested. In Cathemarium malaria, both in canary and duck, it is 3.5 times more active than mepacrine. Different tests against galinaceum malaria show it to be 5 to 13 times as active as mepacrine. In lophirae malaria in

the duck it is 2.5 times as active as mepacrine. Like mepacrine, chloroquine does not produce permanent cures in any of these infections nor is either drug prophylactic in sporozoite induced cathemarium malaria in the canary or gallinaceum malaria in the chick.

Chloroquine is highly active against the erythrocytic forms of *P. vivax* and *P. falciparum*. It does not prevent relapses in vivax malaria even when administered in doses many times those required to terminate an acute attack nor will it prevent the establishment of vivax infection when administered as a prophylactic.

It is highly effective in vivax malaria as a suppressive agent and in termination of acute attacks, significantly lengthening the interval between the treatment and relapse beyond that observed with mepacrine or quinine. In falciparum malaria it has been demonstrated to suppress the acute attack and to effect complete cure of the infection. Studies of the anti-malarial activity of chloroquine against well standardised strains of *P.vivax* and *P. falciparum* have shown its activity to be approximately three times that of mepacrine. In well tolerated therapeutic doses a great majority of patients will be afebrile within twenty-four hours and the remainder will be afebrile within forty-eight hours. Thick smears for parasites will generally be negative in forty-eight to seventy-two hours.

Recommended Dosage:

A. For Suppressive Therapy: A dose of 0.3 gm. given on the same day each week has been found to be effective and is recommended.

B. For the treatment of the acute attack: An initial dose of 0.6 gm. of chloroquine should be given and a further dose of 0.3 gm. 6 to 8 hours later. Alternatively 0.3 gm. may be given every six hours during the first twenty-four, making a total of 1.2 gm. 0.3 gm. should be given in a single dose in the morning for the next two days. This regimen lasting for four days will be adequate to produce cure in cases of *P. facliparum* and terminate an attack of *P. vivax*. Symptoms and parasites in the blood disappear completely.

Chloroquine has been tried in the treatment of the acute attacks of *P. vivax* malaria by Most *et. al.* (1946). His patients were military personnel who had acquired Vivax infections in the Pacific or Mediterranean war zones. These patients, during acute clinical attacks, were divided into three groups; each one was given different schedules.

Treatment Schedules:

In Plan A, 1.0 gm. was given in one day in does of 0.4 gm., 0.3 gm., 0.3 gm. at 8 a.m., 12 noon and 5 p.m respectively.

In Plan B, 1.5 gm. was administered in the course of four days, two doses of 0.3 gm. being given on the first day, and one dose of 0.3 gm. daily for the three succeeding days.

In Plan C, 2.0 gm. was given during seven days; the first day 0.4 gm., 0.2 gm., 0.2 gm and for the remaining six days 0.2 gm. once a day.

They compared the efficacy of the three drugs (chloroquine Plans A,B,C, Mepacrine 2.8 gm in seven days and quinine 30 grains per day for fourteen days) as regards the rate of disappearance of parasites from the peripheral blood during the administration of the drugs and found that the peripheral blood becomes free from parasites more rapidly with chloroquine than with either of the other drugs: the difference was more marked between chloroquine and quinine than between chloroquine and mepacrine. This superiority was evident in Vivax malaria of Mediterranean or of Pacific origin in first attacks as well as in relapses occurring at any stage of disease.

They also found chloroquine more effective than quinine or mepacrine in controlling fever during treatment of acute attacks of Vivax malaria. The temperature comes down to normal the next day and only in 2.1 per cent of cases was there a high temperature on the 2nd day while with quinine or mepacrine there was fever on the 2nd or 3rd day in 8.7 and 8.0 per cent of cases respectively. In controlling the symptoms of malaria chloroquine is at least as good as quinine or mepacrine and is superior to one or the other in the control of some symptoms. Headache and backache are relieved more rapidly with chloroquine and quinine than with mepacrine. Quinine is more effective than mepacrine in the control of generalised aching but is not significantly better than chloroquine. Weakness, dizziness and light headedness disappear more readily with chloroquine or mepacrine than with quinine. Nausea persists longer in patients treated with the other two. The effect of each of these drugs on the duration of vomiting, abdominal pain and abdominal tenderness is essentially the same.

Toxicity.—In 365 patients Most. *et el.* (1946) who were administered 0.8 gm. to 2.0 gm. in one to seven days there were no major toxic effects. When the drug was taken on an empty stomach occasional mild nausea was observed. Dizziness and light headedness were rarely noticed. There were no tinnitus or visual disturbances. About 20 per cent of 284 patients treated with chloroquine developed pruritus during the course of treatment. Pruritus was usually localised on the palms and soles but occasionally it was generalised. It occurred frequently within the first two days of treatment but it was slight and transitory. In some there was erythema or mild papular eruption.

Most. *et al.* (1946) opined that there were no significant symptoms of toxicity from chloroquine. In comparing chloroquine with quinine and mepacrine they say that chloroquine does not produce the disturbing symptoms of cinchonism produced by quinine and that it

is just as safe as mepacrine. Further, they consider chloroquine preferable to mepacrine for patients with eczematoid dermatitis or atypical lichen planus, in whom the administration of the latter may produce an acute exacerbation of the dermatitis. They have never found any flare up of the underlying dermatitis of the patients treated with chloroquine.

Effects of drugs on interval prior to relapse following treatment.—In treating 500 patients with acute attacks of Vivax malaria of Pacific and of Mediterranean origin Most, *et* (*loc. cit.*) found a relapse rate of from 75 to 85 per cent for the former and 35 per cent for the latter. They followed these cases till they had a relapse or for a minimum period of one hundred and twenty days. Quinine, mepacrine hydrochloride and chloroquine do not materially influence the ultimate rate of relapses following the treatment of an acute attack. The rate of relapse is neither influenced by the age of the disease, the number of previous attacks, the total amount of drugs administered or the duration of treatment. Cases treated with quinine, mepacrine and chloroquine had a relapse rate of 85, 80 and 70 per cent, respectively, during the period of observation of one hundred and twenty days. They have found that of the number of relapses which occur within one hundred and twenty days more than three-fourths will take place in first fifty days after treatment with quinine, while only one-half and one-sixth will take place in the same time after treatment with mepacrine hydrochloride and chloroquine, respectively.

None of the drugs so far available produce complete cure of Vivax malaria. The choice of drugs should be on the basis of length of interval between the relapses Most, *et al* (1946) feel that in all these respects the interval before relapse after treatment with chloroquine will be on the average at least five weeks longer than that after quinine and about two weeks longer than that after mepacrine hydrochloride. Only a negligible number of patients treated with chloroquine will have relapses during the first fifty days after treatment. Thus not only does chloroquine promptly control symptoms, fever and parasitemia, but in addition spares the patient from another attack for a period of about two months.

It is suggested that the acute attack of vivax malaria and *P. falciparum* be treated routinely as follows :—

One tablet (0.3 gm.) of chloroquine is to be administered when diagnosis of Vivax Malaria is established by a positive blood smear. This amount of the drug (0.3 gm.) is to be repeated four hours after the first dose. One tablet (0.3 gm.) is then to be given on each of the following three mornings, the total dose is five tablets totalling 1 5 gm. of chloroquine administered during four days.

PLASMOCHIN

Plasmochin, (Pamaquine, U.S.P., Pamaquin, B P., Praequine, French) was introduced by German workers in 1924. Cilional was

another similar drug introduced in 1938 by the Germans and was supposed to be more potent than plasmochin but was never released for general use. The manufacturers claimed plasmochin to have both schizonticidal and gametocidal action and hence claimed that it would eradicate malaria. It cured clinical attacks of malaria (*P. Vivax and P. Malaria*) but only when given in doses which proved to be highly toxic in the majority of cases. It did not have any effect on the clinical course of *P. falciparum* but killed its circulating gametocytes. However, its gametecidal action was possible with small and perfectly safe dosage.

Absorption and Elimination.—It was absorbed in a short time and began to appear in the urine within 20 minutes of administration. Only a small portion was excreted the bulk being destroyed in the tissues. The effective blood level has not been estimated. Toxic effects (West and Henderson, 1946) have been noticed from the time of introduction. They are (*a*) abdominal pain, vomiting, jaundice ; in fatal cases hepatitis, fatty degeneration or necrosis of the liver ; (*b*) headache, general weakness, anaemia, collapse and drug fever ; (*c*) cyanosis and livid discolouration of lips and of the whole skin. Methoemoglobinuria and cyanosis of the lips are considered indications to the stop the drug.

Clinical Experience.—The mode of action is not definitely known but is probably by reducing the rate of reproduction. In a schizonticidal dose it has been proved too toxic for general use and as such it has been given up as impracticable in the clinical cure of the acute attack. Even in a smaller dosage combined with quinine or mepacrine it has not proved useful. Its value lay in reducing the number of relapses in benign tertian malaria. 0.01 gm. twice daily for three days would destroy or sterilize the circulating gametocytes, particularly in malignant tertian infection. In the treatment of relapsing P. vivax a quinine-plasmochin combination has been less toxic than that of mepacrine-plasmochin and has been more effective than mepacrine alone (*War Office Bull.*, 1945).

Plasmochin has the unique property of destroying gametocytes not possessed by other antimalarials, but gametocyte destruction is not a measure that in any way aids the patient. It may be considered in certain circumstances to assume an important position as prophylactic measure for the general population in a malarious country. But this action of plasmochin has not proved so far of any practical value. Clark and his group (1941) arrived at the conclusion that plasmochin had contributed relatively little to effective symptomatic relief. Similar doubts regarding the prophylactic value of its gametocidal effect in controlling malaria in endemic areas have also been expressed by others.

It is hoped that the new drug pentaquine, a drug belonging to the same quinoline group, and which is described below, will be more useful.

PENTAQUINE

Pentaquine (Loeb, 1936) (SN 13,276) is 6-methoxy-8 5-isopropylaminoamy-lamino-quinoline.

It is drug similar to pamaquine. It is absorbed rapidly and completely from the gastrointestinal tract. In experimental animals pentaquine closely resembles pamaquine naphthoate with respect to absorption, excretion and tissue distribution. The difference being that the plasma level of pentaquine is sustained somewhat longer than that of pamaquine. The toxicity of the drug in adult human beings is qualitatively the same and quantitatively approximately one-half to three-fourths that of pamaquine The toxicity is not increased by simultaneous administration of quinine. The toxic symptoms are anorexia, abdominal discomfort or pain, slight methaemoglobinuria, postural hypotension and drug fever.

The antimalarial activity of pentaquine is similar to pamaquine but is effective in a smaller dosage. Pentaquine will partially cure a clinical attack of malaria when given in a large dose of 120 mg. base, but will also produce toxic effects and hence it is not recommended. The same toxicity will prevent its use in prophylaxis or in prolonged suppression of malaria The recommended dosage in the cure of malaria caused by *P vivax* is a daily dose of 60 mg. base (equivalent to 80 mg of diphosphate) and 2 gm. (30 grs.) of quinine, administered concurrently in divided doses every four hours for fourteen days. This is sufficient to produce a radical cure of severe infections due to *P. vivax*. The daily dosage of 60 mg. base should not be exceeded. Treatment may have to be continued for a greater number of days in non-immune persons particularly if they are heavily infected. It is advisable that pentaquine be administered only under close medical supervision preferably in the hospital.

Its toxicity in children and coloured people has not been determined. In pentaquine we have a drug which will replace plasmochin in reducing the rate of relape of *P. vivax* infection in combination with quinine, because of its lesser toxic effect. Though pentaquine is under clinical trial, it is hoped that a further search for a drug of lesser toxicity is being made.

CONCLUSION

Mepacrine was considered as a valuable addition to the armamentarium of the physician for the cure and suppression of malaria until 1942, but quinine had the pride of first place. Recent work has shown that mepacrine is a valuable drug in the fight against malaria. Despite the fact that quinine and other cinchona alkaloids have now had to take a place below mepacrine on the antimalarial list, recent work has in no way questioned their efficacy. On the contrary it has confirmed previous work regarding the antimalarial activity of all the crystalline alkaloids, and more especially that of a mixed alkaloidal preparation, which in some poor malarious

countries may, on economic grounds, still prove to be the drug for choice for the masses.

Paludrine, a new British antimalarial, has been extensively tried and is as effective as a drug as mepacrine both in clinical attacks and as partial casual prophylaxis against *P. vivax*. It is non-toxic except in large doses which occasionally cause nausea and vomiting. Effective dosage is much smaller. There seems to be little to choose between single doses of paludrine and mepacrine in the treatment of the acute attack of relapsing or delayed primary benign tertian malaria, apart from the slight abdominal discomfort sometimes produced by the latter. The advantage of paludrine lies in the fact that it does not colour the skin and hence is a more satisfactory preparation to prescribe over a long period. The action of paludrine is not confined to the erythrocyte form of parasite as with mepacrine but also on the exoerythrocyte form of P. falciparum and partially on exoerythrocytic forms of P. vivax. It is possible that if paludrine (0 1 gm.) is given in a twice weekly dosage over a prolonged period it may affect the relapse rate of chronic B. T. Malaria, upon which mepacrine has little effect. This period is yet to be defined.

Chloroquine, an American synthetic drug, is a highly effective and safe antimalarial. It is considered superior to quinine and mepacrine in the treatment of acute attacks of malaria. It is more effective than quinine, mepacrine and paludrine even when administered in relatively smaller doses over a shorter period of time. Staining of skin, too, does not occur because it is colourless. But even though the occurrence of relapse is delayed much longer than with quinine or mepacrine it has no complete casual prophylaxis against *P. Vivax* and hence it does not diminish the rate of relapse. Chloroquine is a promising drug but it is still under clinical trial and it is worthwhile awaiting the results of further tests before coming to final conclusions.

The strict limitations of plasmochin in the treatment of malaria have long been recognised and recent work has merely served as a reminder of these. It is, however, the only drug that acts as a true causal prophylactic and actually prevents relapses in benign tertian malaria, albeit in large and dangerous doses. These unique properties should be remembered and in special circumstances advantage should be taken of them.

Pentaquine is a new drug of the same series and is equally effective with less than half the toxicity. This drug is under clinical trial and let us hope that it will replace plasmochin and be useful in preventing relapses of *P. Vivax*.

The intensive chemical and medical research that is now being pursued in various countries in search of new synthetic drug may lead to the discovery of a drug which is a complete antimalarial

and at the same time non-toxic. However, at present, we have in paludrine a drug of better promise than any other antimalarial known so far. Chloroquine, from the work published so far, has a similar antimalarial property but has the advantage over paludrine in having a shorter therapeutic regimen. One must await further trials before assessing its place among the antimalarials.

Drugs alone will not be able to banish malaria. But with their help, it will be controlled in certain areas where hitherto this was impossible. Where a measure of control has already been attained these drugs will aid in making it more effective at a lower cost. Malaria incidence may be still further reduced by the destruction of the mosquitoes by the use of insecticides like DDT assisted by the suppressant action of antimalarial drugs.

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LEUCORRHOEA

S. N. GARDE

Bourne and Williams give the following definition: "Leucorrhoea may be a functional excess of the normal secretions of the cervix and vagina or the existence of white discharge containing pus and other abnormal elements due to an infection". Women's ideas vary considerably as to what is normal. It is, therefore, necessary to regard the disease objectively and form one's own idea about its clinical existence.

It must be realised that leucorrhoea is a symptom and not a disease. Although in the vast majority of cases it has its origin in lesions of the reproductive organs, it may also originate from a variety of systemic conditions. Therefore it behoves the gynæcologist to make a thorough general examination. The commoner conditions in one's experience are general debility, chronic amoebiasis, anaemia and vitamin B deficiency.

Vitamin B deficiency deserves to be discussed in some detail as it is the result of the present-day food situation. Cases of this nature were non-existent in England before the war. but they are not uncommon now. One finds the same tendency here. Before the war these cases were confined to the hospital class of patients. But at present they are seen in private practice, not only in the middle but also in the upper class of patients. Recently we have had patients who have done well on vitamin B therapy alone. Braun, Bromberg and Brezenski are of the opinion, that riboflavin deficiency is the principal factor in the causation of vulvo-vaginitis and other symptoms. They claim they have had better results with riboflavin alone than with vitamin B complex. One has had no experience of treating such patients with riboflavin alone. In one case the treatment was attempted but not continued for long and was changed over to B complex with good result. Aneurin or nicotinic acid alone have also been advocated. Our present practice is to prescribe vitmin B complex parenterally and then to put the patients on yeast tablets—Squibb's or Phillip's—6 to 8 per day. There is no doubt that the administration of the whole B complex is a wiser procedure than the using of any one of the components thought to be deficient. The deficiency is seldom, if ever, so clear cut. It is always multiple. Since this condition is the result of the present-day food situation, the real solution of the problem lies in it improvement.

Before leaving the subject of systemic conditions and starting with the investigations, it should be emphasised that leucorrhoea properly investigated, may lead to the diagnosis of serious lesions such as tuberculosis, syphilis, new growths and many others. Leucorrhoea may be the only apparent symptom.

EXAMINATION AND INVESTIGATIONS

I. Age.
II. General examination.
III. pH reaction of the vaginal and cervical secretions.
IV. Routine gynaecological examination.
V. Gram-stained smears. cervical, vaginal and urethral.
VI. Kahn or Wassermann tests.

I. Age:

A.—Children: Nearly all cases are of vulvo-vaginitis. The most important investigations should be directed towards the establishment of Niesserian infection, next to the exclusion of worms. The history of the child passing worms is useful. Irritation of anus is very suggestive and examination of the stools conclusive. Occasionally trichomonas, thrush or diphtheria may be responsible.

B.—Adults of Child-bearing Age: The large majority of cases are cervical in origin, though trichomonad vaginitis and gonococcal vulvovaginitis (vulvitis in the non-pregnant and vulvo-vaginitis in pregnant women) are not uncommon. In pregnancy and diabetes, monilia and allied fungus infections are not uncommon. In fact some authorities estimate that 25% of pregnant women suffer from mycotis infection. The writer's experience is the same. Patients suffering from virginal leucorrhoea will also come under this age period.

C.—Post-Menopausal: Here vaginits due to pyogenic infection is commonest lesion. Occasionally trichomonas and rarely gonococcal infection are met with. Cancer, of course, must be kept in mind, though one is inclined to agree with Curtic when he states "that the importance of leucorrhoea as a diagnostic symptom of early cancer has been overstressed".

II. General Examination:

The general examination of the patient is of course important. It is stressed here on account of the systemic conditions that may give rise to leucorrhoea and also because of the tendency on the part of a busy practitioner to skip it.

III. pH Value:

The normal pH value of the vagina is from 4 to 4.5. A simple method of estimating the pH value is by the nitrazine test papers. These papers and the coloured chart for comparison are prepared by Squibb & Co, Though available in the United States, they are not yet available here. The agents, however, say that the nitrazine papers and the chart will soon be available. With this method one

can record pH from 4 to 7.5. The writer for the last few years has been using the British Drug House's capillator which records pH values from 4 to 11.

IV. Examination of Fresh Wet Smears:

A drop of normal saline is put on the slide, and a drop of discharge taken from the vagina and/or cervix with a pipette is mixed with the saline. This is examined directly under the microscope with 1/6th lens, without staining. Care must be taken that no antiseptics come into contact with the discharge before this examination. It should, therefore, be done before the bimanual examination. This is a most useful and simple procedure in the investigaion of leucorrhoea. It is particularly useful in the diagnosis of trichomonas, local amoebic, monilia and allied fungus infections. It may sometimes be profitable to stain the discharge with methylene blue particularly where mycotic infection is suspected.

V. Bacteriological Examination:

Examination of smears from the vaginal, cervical and urethral discharges by Gram staining is desirable in every case of leucorrhoea and essential when clinically and from the history gonorrhoea is suspected. A history of gonorrhoea in the husband is of great significance, even if he has been treated and thought to be cured both by the physician and the man himself.

Smears examined microscopically will fall into one of the three grades:

GRADE I: Large number of epithelial cells and Gram positive acidophilic bacilli. In these cases, even though there may be a profuse discharge there is no infection.

GRADE II: Number of pus cells and enormous masses of cocci both Gram positive and negative and few, if any, epithelial cells, Grade III is a true infection either pyogenic as in senile vaginitis, gonococcal or trichomonad.

GRADE III: Is a mixture of grades I and II. There are occasional bacilli of the acidophilic type and epithelial squames and also pyogenic cocci and leucocytes. Grade II is a mild low grade infection. A few salient features of the various infections will be mentioned along with the treatment under the respective headings.

VI. Routine Gynæcological Examination:

This is of course of the utmost importance.

VII. Kahn or Wassermann Tests:

Syphilis may sometimes cause leucorrhœa. Whenever there is the slightest suspicion of syphilis the blood must be examined.

A case recently under our care well illustrates not only this point but also the importance of thorough investigation in a case of leucorrhœa.

Case Report:

Mrs. M., age 25, Para 2 + 0.

COMPLAINT: (1) arthritis both knee joints. Unable to stand. Duration 3 weeks.
(2) Leucorrhœa.

BRIEF HISTORY OF PRESENT ILLNESS: For the last 3 weeks the family physician was treating the patient for? rheumatic or rheumatoid arthritis. As she was not improving a second opinion of a consulting physician was sought. It was at the latter's suggestion that the patient was referred to us in order to exclude the cervix (because of leucorrhœa) as being the septic focus causing arthritis.

Examination of the Patient: Family, personal, menstrual and obstetric history revealed nothing relevant. The husband denied having suffered from gonorrhœa or syphilis. The patient looked ill, thin and anæmic and was unable to stand. The temperature was normal. B. P. 100-70. Urine was normal. Gynæcological examination revealed the presence of yellowish white discharge. This discharge was not offensive or frothy and was non-irritating. pH value of the vagina was 5. Fresh wet smear did not show trichomonas or fungus. Cervical and urethral smears were negative for the gonococcus. Microscopically grade II infection was noted.
P.V. and Speculum Examinations.

Ext. parts. Normal.

Cervix-erosion round the external os, 4 Naboth's follicles.

Uterus: anteverted, anteflexed, mobile.

Fornices: N.A.D.

Because of the symmetrical affection of the knee-joints, in spite of there being no other evidence of syphilis, blood was examined for Kahn and found + + +. The Kahn test was repeated. The patient's and her husband's blood were both found to be + + +. Both the husband and the patient were treated with a course of penicillin and mapharside. The patient did very well on this treatment. Partly because the patient felt well and partly on account of domestic difficulties, the cervix was not cauterised for another 2 months. One is therefore inclined to believe that it could not have been the cause of her arthritis.

This case shows clearly the importance of thorough investigation in case of leucorrhœa. If one had been satisfied with the cervical erosion as the cause of arthritis and a Kahn test had not been done syphilis would have been missed at the time, and perhaps subsequently masked due to administration of penicillin and iodides.

Treatment:

Before discussing the treatment under the various headings, a word must be said about the general management of these patients. The general state of the health must be attended to. For local cleanliness a vaginal douche is advised. The chemicals used for sdouching are too numerous for enumeration. Our practice is to

prescribe either dettol, one tea-spoonful to a pint of warm water, or soda bicarb, and sodium chloride, one tea-spoonful each to a pint of warm water. Where the discharge is purulent or sticky the latter is chosen, otherwise the former. It is immaterial what chemical is used for douching. But what is important is to specify the strength of the chemical to be used, as it is rather common for women to use unnecessarily high strength, which probably do more harm than good. On the whole it is wise during pregnancy to avoid a vaginal douche and, if needed, it should be a low one. the can being placed not higher than a couple of feet. It is a popular misconception that a douche should not be taken during menstruation.

Vulvo-vaginitis of Children:

Schaffler et al. who studied 256 cases of this type with different treatments both local and general—silver nitrate ointment locally, Metaphen and Acriflavine (1 : 500) suppositories, Azochloramide in oil, cold quartz light, Theelin (P.D. & Co.) Amniotin (Squibb's) sulfonamides—came to the conclusion that silver nitrate ointment gave the best results and sulfonamides the next best. They found œstrogenic and other therapeutic agents unsatisfactory.

Before the advent of penicillin the arguments regarding the treatment of this condition raged around the comparative values of œstrogenic treatment (parenterally and or locally) dextrose suppositories and sulfonamides. The advisibility of not using œstrogens in the child is evident. The superiority of penicillin over the sulfonamides is well established. Now that penicillin is freely available there is no doubt that it is the best treatment, both parenterally and locally. For local use Ca Penicillin 500 units per c.c. should be used.

Where the cause is worms, of course, the patient must be treated accordingly.

Virginal Leucorrhoea:

These cases are non-infective in origin. Bourne thinks they are due to hyper-œstrinisation of the cervix, a sort of trachellopathia. Such patients as one has seen have not been examined bimanually or per speculum. One is not therefore in a position to say from one's own experience what the cervix feels or looks like, whether the so-called congenital erosion is present or not. It has also struck one that none of the patients seen, had any other symptoms of excess of œstrin. Those few patients who had to be curetted for puberty menorrhagia invariably had a normal looking cervix. The patients seen had been in poor health, without exception. Therefore, without denying the possibility of congenital erosion as the ætiological factor one is inclined to the view that poor health is more important. It might be mentioned that the possibility of masturbation should be kept in mind, particularly where the labia minora are found to be hypertrophied. The history in these cases is fallacious.

If at all one examines these patients gynæcologically, it must be done under anæsthesia.

Treatment is entirely on general lines with injections of liver extract, with vitamin B complex and iron by mouth.

Endocrine treatment has proved entirely disappointing. The hormone mostly tried was progestin. Bickers however, advocated thyroid extract in these cases on the assumption that it may act as an anticestrogenic, an assumption difficult to believe.

If it is decided to examine the patient under anaesthesia it would be wise to keep the cervical dilators and the electric cautery ready, so that in case the so-called congenital erosion was discovered one could at once proceed with dilatation up to Hegar No. 4 and cauterisation. That would spare the patient another anæsthetic.

Child-bearing Age:

(1) *Cervicitis*: Cervical infections may result from primary invasion by the gonococcus or may be caused by invasion of pyogenic organisms, post partum, post abortum, or after instrumentation.

Acute Stage: The treatment of leucorrhœa in these cases is over-shadowed by the treatment of the causal factor. Penicillin and sulfadiazine are of the utmost value. For the relief of pain, sitz baths and opiates are used. Fowler's position for drainage and low vaginal douches and glycerine-mercurochrome installation for cleanliness are useful measures.

Chronic Stage: In the chronic stage the treatment is topical either by application of silver nitrate, mercurochrome, etc., or the electric cautery. The writer agrees with Bland and Rakoff that these applications are of very limited use. The writer has now completely discarded these applications.

The electric cautery is undoubtedly the best treatment for chronic cervicitis. There are various techniques used in cautersing the cervix. The one the writer has found most useful is to make 5-6 linear strokes a couple of mm. apart starting from a little inside the external os and extending to the whole extent of the erosion and separately puncturing the Nabothian follicles. Where endocervicitis is suspected it is wiser to dilate the cervix and then cauterise, to avoid any danger of stenosis resulting in hæmato—or pyometra. As a rule cauterisation can be performed without any anæsthesia. Occasionally one does come across patients who demand an anæsthetic. Plugging the vagina with pantocaine 2 per cent for 5 minutes serves the purpose admirably. If the patient insists on being put to sleep gas, trilene or sodium pentothal may be used.

The precautions to be taken are, to avoid sepsis by the application of pure Dettol before starting the cautery, and a thorough cauterisation. For avoiding hæmorrhage which may occur on the 6th or 7th day, rest in bed is advised. The patient must be

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advised to take a douche daily and come again after two months. Extensive erosions may need another cauterisation, which is done after two months.

Cauterisation will not be an adequate treatment in cases of extensive erosion of the cervix or endocervicitis. Here the choice of treatment is between conisation, as advised by Crossen or surgery, either a trachelorrhaphy or amputation of the cervix. The writer has no personal experience of conisation and has invariably resorted to surgery.

Trichomonas infection:

Trichomonas infection is very common in the western countries. It is not so common here; this is hard to explain. Green-Armytage who has had extensive experience, both in the East and the West, attributed the higher incidence in the west to the extensive use of contraceptives.

The only certain way of making a diagnosis of trichomonas infection is by finding it in the discharge examined microscopically. Repeated examinations are often necesssry before finding it, and examinations soon after the period are more likely to be successful. One can, however, diagnose the condition with a fair amount of accuracy clinically. A foul smelling purulent discharge, greenish yellow in colour and often frothy accompanied by pruritus vulvae and tenderness in the vagina with punctate haemorrhagic spots, is very suggestive of trichomonas. These patients often complain of dysuria and dyspareunia. Resistance to treatment and recurrence is almost pathognomic.

Treatment:

The treatments recommended for this condition are legion. That alone shows that the treatment is unsatisfactory. Almost any treatment cures the patient so long as the treatment lasts. Recurrence is the real problem.

The treatment described here and at present followed by the writer is based on the treatment practised at the Lahey Clinic with slight modifications. The patient is given the following instructions:

(1) At bed time take a douche of 2 quarts of warm water into which are added 3 ozs, of ordinary household vinegar. The douche is best taken lying down and in such a way that the vagina is distended every now and again.

(2) After the douche introduce a Desulan tablet high into the vagina and leave it there Desulan tablets contain sulfonamide, Pyridine, mercuric chloride, lactose and carbohydrates.

(3) Do this every might for six weeks and every other might for the next six weeks.

(4) During each day of the menstrual period take the douche in the morning and at bed time and insert two tablets into the vagina

(5) Once a week during this treatment the Vagina is insufflated with either Cade's on John Wyeth & Co.'s insufflator the powder used for insufflation contains kaolin, acriflavine and sulfathiazole. When silver picrate was available the powder used was equal parts of silver picrate and sulfathiazole. Before insufflating, the vagina is cleaned with hydrogen peroxide and dried. There is no danger in vaginal insufflation. The three fatalities reported by Brown, Pierce and Patridge, were all cases of pregnancy. Pregnancy is an absolute contra-indication to vaginal insufflation. Menstruation and vaginal bleeding are also contraindications.

The writer has had very satisfactory results with this treatment. He is aware that the number of cases (four) thus treated is small, and, what is more important, the time that has elapsed since the completion of treatment is too short to correctly assess the value of this treatment. Nevertheless there is no doubt in one's mind that this is so far the best treatment.

Bohme gives the following causes for failure of this treatment:

(1) Improper taking of the douche.

(2) The tablets either were lost or were introduced in such a way that they did not dissolve.

(3) Some patients cannot overcome their dislike to douching during the period.

Amoebic Vaginitis:

Is clinically very much like trichomonas but not so severe. The diagnosis rests on finding the amœbæ in the discharge. The writer has seen two such cases. The treatment is on the same lines as trichomonas except that in addition to the local treatment the general treatment for amœbiasis must be given. In future it is proposed to treat these cases with vioform and sulfathiazole powder insufflation.

Mycotic Infection:

This is common in pregnant and diabetic women, in the former due to lactosuria, and in the latter due to glycosuria. It is however, not uncommon in the nonpregnant and nondiabetics.

The characteristic clinical picture is the presence of discharge which is usually scanty and curdy. The patient complains of pruritus but not to the same extent as in trichomonas infection, and sometimes of soreness of the vulva.

The diagnosis is of course made by the microscopic finding of the hyphae and blastomeres mixed with pus and epithelial cells.

There are numerous treatments in use. Gentian violet is undoubtedly the drug of choice. Solutions both aqueous and alcholic, in strengths varying from 1 to 5% have been recommended. Two per cent aqueous solution has given very satisfactory results in one's experience. Bland and Rakoff prefer equal parts of gentian violet and acriflavine 1%. Where diabetes is present of course it must be treated.

Foreign bodies:

The varieties of foreign bodies causing leucorrhoea is of course legion. Foreign bodies are introduced by the physician or the patient herself. The foreign bodies commonly found in practice are (1) Neglected pessaries. Time and again one sees patients with pessaries, who have not taken a douche, either because the attending physician did not advise them to do so or because of carelessness in carrying out of the instructions. (2) Neglected vaginal plugs. Neglect either on the part of the doctor, nurse or the patient herself. (3) "Lost tampax"—"And I thought I had dropped it," is what the patient said when it was removed. (4) Hysterical women and sexual perverts may use any sort of article for their satisfaction.

The treatment in all these conditions is evident.

The discharge following fistulae is self-evident; The treatment is surgical.

Senile Vaginitis:

This is endocrinal in origin. Due to hypo-estrinisation atrophic changes occur in the vagina in the post menopausal period and make the patient vulnerable to non-specific infections resulting in purulent discharge. Pruritus usually is a prominent symptom. One must of course beware of cancer at this age period.

Estrogens are a specific remedy for this condition. The best way is to administer stilboestrol 0.5 to 1 mg. a day orally and also to use vaginal suppositories, The patient must be warned against the oestrin withdrawal bleeding which may unduly alarm her.

(*Indian Journal of Medical Sciences. Aug. 47.*)

SURGICAL TREATMENT OF MENIERE'S DISEASE IN A DEAF-MUTE

Jame O. Gooch, M. D., Fellow in Otolaryngology and Rhinology, Mayo Foundation and Olav E. Hallberg, M. D., M. S. in Otolaryngology and Rhinology, Section on Otolaryngology and Rhinology:

A twenty-three year old man registered at the Clinic on March 29, 1946. He complained of episodes of dizziness, nausea and vomiting that had been present all his life. He said the episodes had occurred more frequently during the four years prior to his registration. He had been born deaf by normal delivery. Forceps had not been used. Quinine had been used during the mother's labour. She had measles during pregnancy.

The patient's adjustment to life apparently had been good. It had been aided by his attendance at an institution for deaf-mutes until the age of nineteen years. He had married a deaf-mute one year prior to his registration at the Clinic. Because of the frequency of occurrence and severity of the attacks, the patient became unable

satisfactorily to work at his job as a printer's helper; hence, he sought advice at the Clinic.

At the age of seven or eight years, while the patient had been playing with other children, vertigo appeared suddenly, causing him to fall down and vomit. He had remained dizzy and nauseated all that day. Episodes such as this one recurred at intervals of one year to five years until four years prior to his registration, when they began to appear once or twice a week. The condition was characterized by vertigo, diplopia, bilateral tinnitus, nausea and vomiting. Vertigo was of such severity that he would fall down. Symptoms ordinarily persisted for a day or so, but he had obtained practically no relief for two weeks prior to registration.

Psychogenic factors were those which might be expected in a deaf-mute subjected to additional stress by the fact that his wife was pregnant and that he was unable to work. His mother, who accompanied him, said that as a boy he always had been nervous and high strung.

Results of the general, neurologic and otolaryngologic examinations were essentially negative, except for very little reaction in response to caloric tests of both static labyrinths. The result of urinalysis was negative. The value for hemoglobin was 12.5 gm. per 100 c.c. of blood and the leukocyte count was 8,400 per cubic millimeter of blood. Results of roentgenograms of the stomach, thorax and mastoid processes were negative. A roentgenogram of the head showed a bridged sella turcica.

Conservative measures where begun on April 4,1946. Prior to that time vertigo and nausea had developed for the first time while the patient was under observation. Fifty milligrams of benadryl were slowly administered intravenously. The effect of this measure was only mild aggravation of symptoms. Pyribenzamine hydrochloride and histamine diphosphate were as poorly tolerated as benadryl had been

On April 11, 1946, with the patient under the influence of regional and intratracheal inhalation anesthesia with nitrous oxide-ether and oxygen as the agents, bilateral labyrinthotomy was performed. The postauricular approaches and the operative technic evolved by Lake and Milligan, and later modified by Day, were employed. On each side the well-aerated mastoid processes were exenterated, so that the inci were exposed. Large fenestrae were made about 2 mm. posterior to the surgical domes of the labyrinths. A small, curved platinum electrode was introduced into each vestibule and diathermy was applied. In the application of diathermy, the current was sufficiently strong to cause some twitching of the facial muscles, but facial muscular weakness did not appear subsequently. The cavities were lightly dusted with sulfanilamide powder and closed with zytor and black silk sutures. One small soft rubber drain was placed at the interior extent of each wound.

Postoperatively, 160,000 units of penicillin was administered daily as a prophylactic measure. Vertigo and nausea, although they were rather severe immediately postoperatively, diminished daily. Supplementary fluid, administered intravenously to the extent of only a liter a day, was required for the first three days of eleven day hospitilization period. Sutures and drains were removed on the fifth postoperative day. The wounds healed by first intention.

The condition of the patient was observed for a week after he was released from the hospital. Constant improvement in all subjective sensations was noted and the patient's ability to take care of, and provide for, himself was increasing with mounting confidence. A communication from the patient received nine months postoperatively revealed that he was working constantly, and that from time to time he was subject only to very mild sensations of dizziness of diminishing intensity. The sensations of dizziness were not accompanied by nausea and other distressing symptoms. The patient had some difficulty in vision typical of anyone who has sustained loss of labyrinthine function. This difficulty was characterized by an unusual type of nystagmus and a tendency to overshoot when the patient turned the eyes from any position back to directly forward. This continued briefly, in pendulum-like fashion, until the eyes came to rest on the fixation object. This would account for some of the diplopia experienced when the patient moved his head or when he was walking.

In this instance we had no way of knowing on which ear to operate, because the patient had no symptoms referable to one ear. Surgical treatment finally was decided on with great trepidation; first, because Meniere's disease is rare among persons of this patient's age and second, because so many psychogenic factors might be present in a deaf-mute. We emphasized to the patient the fact that as a result of the surgical treatment he would experience some discomfort, but that it probably would be much less than before. The good result remaining after nine months of observation bore this out, the most important factor being that the patient was able to work steadily.

Only one similar case has been reported, by Dandy. His patient was a male deaf-mute twenty-two years old The audiogram, however, revealed some degree of hearing, although not enough to be of any value to the patient. Dandy's patient had tinnitus in the right ear during attacks and he also had a sensatson of fullness in the same ear. Because of the symptoms, Dandy was able to [illegible] the right eighth nerve in surgical treatment.

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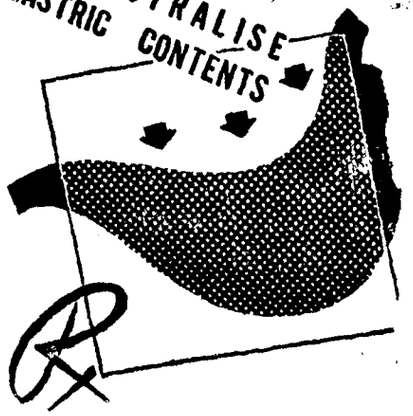

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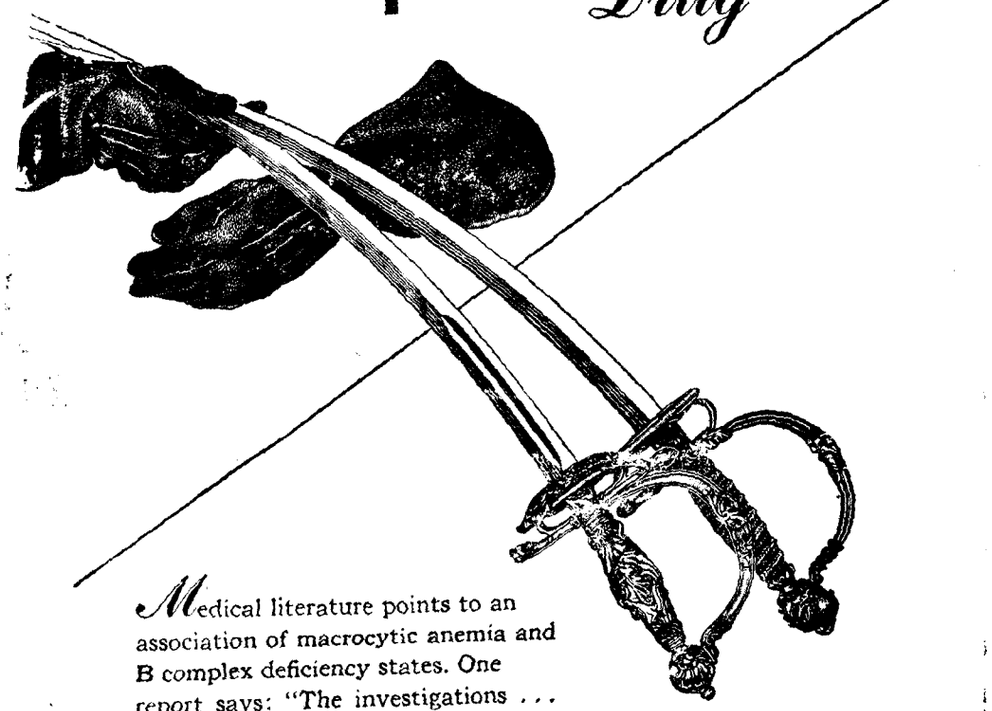

Medical literature points to an association of macrocytic anemia and B complex deficiency states. One report says: "The investigations ... have indicated that a food factor other than the 'extrinsic factor' may also be necessary for the maturation of red blood cells". (1)

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(1) *Spies, T. D. and Butt, H. R., chapter in "Diseases of Metabolism", edited by G. G. Duncan*

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