

BULLETIN

of the

Mahoning County
Medical Society



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—*Oliver Wendell Holmes.*

May, 1936

Volume 6

Number 5



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VOL. VI, No. 5.	CONTENTS	May, 1936
PRESIDENT'S PAGE		136
THE UNHOLY MINORITY		137
NEWS ITEMS		138
BACTERIOPHAGE, WITH SPECIAL ATTENTION TO ITS THERAPEUTIC VALUE		139
DISPLAY PAGE		145
SOME REMARKS ON THE GONOCOCCUS BOUILLON FILTRATE		151
MEDICAL FACTS		153
CHRONIC ABSENTEES		155
SECRETARY'S REPORT		155-156
MISCELLANEOUS ITEMS		

PRESIDENT'S PAGE

The first Mid-Year Organization Conference of the Ohio State Medical Association was held in Columbus, Sunday, April 26th, 1936.

This meeting of local and State medical society officers was arranged at the suggestion of our very able and active secretary, Mr. Charles S. Nelson. The meeting was, of course, authorized by Council and arranged by our State officers. The attendance, at their own expense, of one hundred seventy-five physicians from throughout the state, gathering to discuss some of the problems confronting organized medicine, giving freely of their time and energy, was really a stimulus and a tonic to all concerned. (No; there were no sedatives on the program!)

The stimulus of such meetings will react to the ultimate benefit of each and every member of our organization in a variety of ways. We hope that these meetings will be made an annual event.

Fifteen physicians, the majority of them county officers and committeemen, were asked by our central office to appear on the program to discuss assigned subjects. It is interesting, and greatly encouraging, to note that all fifteen accepted their assignments, were present, and delivered carefully prepared, timely and worth-while addresses. Not without some personal sacrifice could this one hundred per cent result have been achieved. We thank the essayists and all who contributed to this meeting.

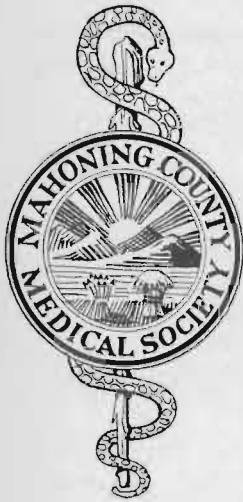
Space does not permit me a detailed listing of speakers and analysis of subjects; for a complete report I refer you to your State Journal. Some observations of personal and local interest were: Seven men attended from Mahoning County—three of these appeared on the program. Dr. Sidney McCurdy appeared hale and hearty, promised a discontinuance of the twenty per cent reduction in industrial fees July 1st, 1936, and asked for the cooperation of the doctors with the commission in the handling of its many cases and problems. Dr. Forman asked material for the Journal; we believe such material is available locally if some of our members will put it in proper shape and send it in. The State Board of Health encourages further and continued efforts in the work of immunization against diphtheria and small-pox; discourages sporadic "summer round-ups," prefers closer personal physician supervision and more accurate, recorded, periodic health examinations.

Discussion of economic problems evoked the most discussion and evident interest. The progress made in the handling of such problems in Mahoning County appears to exceed progress made in most other localities. A motion was passed favoring efforts made to secure compensation for care of indigents, in home or hospital, at fees approximately two-thirds of the usual fees; such efforts to be carried on locally. The rather state wide practice of township trustees failing to pay physicians and hospitals for care rendered indigents was severely criticized. It was pointed out that a revision of the General Code of the State of Ohio as it pertains to health measures and regulations is needed. This is in effect what your delegates to the annual meeting advocated in Columbus in October, 1934.

As we go to press with this resume of impressions of the Mid-Year Organization Conference we earnestly hope that our local Postgraduate Day Assembly, two days hence, may be as much a success in every way as was the Conference.

L. GEO. COE, M. D.

May



BULLETIN

of the

MAHONING COUNTY
MEDICAL SOCIETY

M A Y 1 9 3 6

THE UNHOLY MINORITY

(A Diagnosis)

By L. R. EFFLER, M. D.

There is nothing basically wrong with the practice of medicine either as it now stands or has stood since the beginning of history. The faults are incidental. They may be extrinsic and intrinsic. Extrinsic faults, such as unemployment, unequal distribution of wealth, and the like, are of an economic nature over which the profession has no control. Intrinsic faults of which it does have control, are limited largely to comparatively few doctors and could be entirely eliminated. If faults were corrected, there would be practically no ammunition left for socially-minded reformers of Medicine.

Doctors! quit blaming social workers, public health agencies, and highly endowed foundations for all our troubles! Place some of the blame on our own shoulders! Hold the mirror up to nature and see ourselves as others see us!

Begin with an assumption. Consider roughly that 75% of our practitioners are conscientious and reflect credit upon themselves individually as well as on the profession as a whole. This proportion may not be accurate,

but let it serve for the sake of argument.

What about the remaining 25% of our practitioners? We believe that many, but not all, belong to a class of "rugged individualists" actuated almost solely by motives of self-interest. Their self-aggrandizement, social and mercenary, is at the expense of the public whom they serve, and their medical brethren, whom they should consider. These are the fellows who do most of the damage.

The services of the plodding majority we seldom hear about because accepted as a matter of course. The services of the exploiting minority we hear plenty about because they shriek to high heaven and because they are assumed by aggrieved patients to be the methods of all practitioners.

Let us enumerate a few of the outstanding sins of this Unholy Minority.

First, over-charging for surgical or medical services. For instance, insisting that an operation is worth so much, instead of gauging the charge by the patient's ability to pay.

Second, over-treating a case. Dragging it out endlessly so that Medicine is placed in a bad light.

Third, needless operations brought about by exaggerations of the consequences of avoiding surgery instead of a proper exposition of the pros and cons.

Fourth, needless operations brought about through vicious untruths. These are calculated to trade on a patient's fears by painting pictures of helpless insanity, life-long invalidism, and the like, in consequence of postponement.

Fifth, attempting operations or treatments for which the physician has definite inability to qualify.

Sixth, posing as a specialist when training has been inadequate.

Seventh, over-consultation by passing a patient needlessly through a form of clinic-mill.

Eighth, laboratory examinations that may be as unnecessary as they are expensive.

Ninth, the practice of always finding oddities or abnormalities in each patient where none exists.

Tenth, the practice of looking puzzled or scratching the head in perplexity at each new case.

These last two instances may serve to impress the uninitiated patient by appealing to his pride. They are good salesmanship, but bad ethics. They usually result in "making mountains out of mole hills" and at times frighten a patient when he needs mental comfort and bodily relief.

Eleventh, turning a deaf ear to medical economics questions, so vital at present, and pretending an interest in scientific Medicine alone.

Twelfth, playing the hypocrite by prating loudly of medical ethics and posing as a Pillar of Medicine to the laity, while in reality committing in actual practice every one of the 57 varieties of violations of ethics.

Thirteenth, miscellaneous, which include any and all not mentioned above.

Let each of us examine our conscience and find out whether we fall into any of the above categories. Perhaps our sins may seem only venial in our own eyes. Yet they all prove mortal in the aggregate to their fair name of Medicine and to the interest of the majority. The difference between the Unholy Minority and the Holy Majority lies in the fact that the former sins consistently and knowingly while the latter may sin occasionally only and mostly unwittingly.

The Unholy Minority is doing nothing to save Medicine and everything to jeopardize it. It furnishes the fuel for distrust and suspicion. It supplies the objectionable methods which are gossiped about by dissatisfied patients until they reach the ears of reformers and amount to a hue and cry for a change in the present medical system.

—*Bulletin of the Medical Society of the County of Kings.*

NEWS ITEMS

The Mahoning County Medical Society expresses its deepest sympathy to Dr. W. H. Evans upon the death of his father.

Doctors J. N. McCann and R. B. Poling spent a week at Ann Arbor at the University of Michigan, where they attended Dr. F. N. Wilson's postgraduate course in "Electrocardiographic Diagnosis."

Doctors A. M. Rosenblum, T. K. Golden, and M. W. Neidus presented a symposium on "Atrophic and Hypertrophic Arthritides" at the April meeting of the Staff of St. Elizabeth's Hospital.

Mr. and Mrs. W. Dixon Smith announce the engagement of their daughter Claramae to Dr. J. L. Scarnecchia.

May

BACTERIOPHAGE, WITH SPECIAL ATTENTION TO ITS THERAPEUTIC VALUE

By ALBERTA NELSON, A. B., M. S.

The term bacteriophage, literally, "devourer of bacteria," at first sight probably has stimulated the imagination of every worker since its first use by d'Herelle in 1917. d'Herelle states himself that he did not "use the suffix 'phage' in its strict etymological sense of 'to eat,' but in that of 'developing at the expense of'"; while this conveys the same idea, in a remote way, the literal meaning which incites more romantic dreams of the possibilities of such a thing, has been the one to catch the eye first. Unfortunately, this agent or substance which causes transmissible lysis of bacteria hasn't lived up to the super expectations held out for it. Had moderate views been entertained on the subject during the first ten or fifteen years of its development, fancy would not have run riot and a saner, more sensible attitude toward it would exist today. As it is, however, few workers can take a midway stand on the subject. They are either so extravagant in their hopes and in their praise that the stumbling blocks are lost sight of, or they are over critical to the point where the subject is put completely to ridicule. There are, undoubtedly, factors which would seem to indicate that bacteriophage, of necessity, must be strictly limited in any therapeutic use. On the other hand, evidence is put forth with such enthusiasm by some workers as to its beneficial effects in certain circumstances that it can not be dismissed lightly. There is no doubt that whether the agent can be shown to have definite therapeutic or prophylactic properties at all, if only the true nature of the stuff can be arrived at, a great and far-reaching advance will have been made. This last seems almost impossible of accomplishment, however. So far we can only theorize both as to its ultimate nature and mode of ac-

tion. But these uncertainties as to the nature of the material and unwarranted claims for its therapeutic efficacy should not be allowed to cloud the appreciation of its biologic importance.

The Nature of Bacteriophage

It might be well to summarize at the outset, briefly, a few of the better known theories concerning the nature of this lytic principle and its action.

d'Herelle (1), of course, has always contended that bacteriophage is a living autonomous submicroscopic agent, parasitic on susceptible bacteria, growing and multiplying in the process of changing or dissolving bacteria. This theory has not been proven, nor has it been definitely disproven. In favor of d'Herelle's idea is the fact that the lytic agent may be propagated indefinitely in cultures of susceptible bacteria. This is regarded as evidence of multiplication. Phenomena of apparent adaptation, antigenic specificity and analogies to filterable viruses are cited by d'Herelle as additional support for his opinion. d'Herelle's discovery (2) was made at the Pasteur Institute in Paris, but the Institute directors, Professors Roux and Calmette, did not agree with his idea of the living nature of bacteriophage. That is why d'Herelle finally left the Institute to work elsewhere. More recently, in 1933, M^r. Calmette presented to the Academy of Sciences the results of research by Noël Bernard and Guillermin, who have found, in cultures of the cholera vibrio, a precipitable diastase that has the power of rapidly lysing the vibrio. This diastase, which may be destroyed by heat, acts in infinitesimal doses and makes indefinitely active the tubes of physiologic salt solution into which it is successively introduced, as in the transplantation of a bacterial culture. Also, in the same year, d'Herelle (3)

presented a paper before a meeting in Rome to show that every man and every animal has in the intestine a bacteriophage that lives in symbiosis. Its activity is not specific but it has a variable potency. If it is very potent, the bacterium succumbs; if it is less potent the micro-organism may resist it and acquire immunity to it, and then the bacteriophage is destroyed or accommodates itself to a bacteriophagic symbiosis. Recovery from infectious diseases does not result from an immunizing process but from the bacteriophage and from the reactions that it provokes.

A rather interesting experiment has been performed by Gates (4) whose obvious conclusion points to a substantiation of d'Herelle's theory although other interpretations may also be placed on it. It has been shown that bacteriophages are destroyed by exposure in broth, salt solutions, or in agar plates, to total or filtered radiations of the sun or of artificial light sources. Gates found that the incident energies required to kill staphylococcus aureus or to inactivate its homologous bacteriophage, are measured at the various wave lengths of the quartz mercury vapor arc between 238 and 302 millimicron and run strictly parallel, the readings for the staphylococcus aureus bacteriophage being obtained at a uniformly higher energy level. This difference in levels is of less significance than the striking similarity in the shapes of the energy curves, which indicate that the same organic structures are absorbing the radiations in both instances. The results are open to three interpretations, the most obvious being, naturally, that the bacteriophage is a sub-microscopic organism. Again, it is possible that the bacteriophage is a product of its own lytic action on the homologous bacterium and contains the essential structural units which are also destroyed in staphylococcus aureus by the ultraviolet light and thus cause the death of the organism.

A third explanation is that the bacteriophage of wholly unknown nature, is absorbed on staphylococcus aureus material in so intimate a bond that the alteration of this material by irradiation renders the phage incapable of further lytic activity. This last seems to be highly imaginative, however.

Many investigators, like Calmette and Roux, have regarded the bacteriophage as an inanimate substance, an enzyme or activator of an endocellular hydrolytic bacterial enzyme, having its origin in the bacterial cell which it lyses and being capable of lysing other cells, increasing in amount in the process. Many workers have attempted to prove this theory, too. Namely, Bronfenbrenner, Krueger, and Hetter. Twort (5) (who independently noted the lytic principle two years before d'Herelle) has suggested that the filtrable virus diseases of man and animals might be due to a cytophage, and consequently offers the similar conception of an inanimate cytophage which could initiate autolytic processes in cells and be reproduced by the cells which degenerated because of its action.

Krueger, with Tamada (6), counted the number of lytic "particles" in their purified highly concentrated bacteriophage and made parallel determinations of the total nitrogen in this phage. Even without deducting the recognized noncoagulable nitrogen in their control tubes, the total phage-nitrogen was so small as to show that each lytic "particle" could not be of greater complexity than the average protein molecule. From a reasonable standpoint we can hardly conceive of a single protein molecule as a living self propagating biologic entity; at least, such a conception would not contribute to clarity in methods of study but would offer greater temptation to noncritical fantasy and commercial exploitation. This investigation concurs with that made by a group of Russian workers (7). The

latter further have stated that normal bacterial cells can be hyperoxidized by the use of peroxidase plus hydrogen dioxide, one of the oxidation products being an artificial specific bacteriophage. They found this oxidation product transmissible to new bacterial cultures, where it multiplies (or is multiplied) and produces "lysis" in a manner apparently identical with that of the corresponding natural bacteriophage. Like natural bacteriophage, the artificial oxidation product does not multiply (or is not multiplied) in the presence of dead bacteria.

These two conceptions are the most popular, although the weight of opinion at present seems to be preponderantly on the side of the argument that the lytic principle is inanimate. The difficulty in making crucial experimental tests of these hypotheses comes from the fact that the lytic principle cannot be propagated apart from the living bacteria on which it acts.

Two other theories are usually considered in a discussion of this sort, that of Bordet and that of Hadley. The former (8) believes the lytic principle to be a substance derived from the bacterial cells as a result of some vitiated metabolic process which brings about early death and autolysis of the cultures. This tendency to rapid autolysis may be transmitted from generation to generation by heredity and autolysis of the cells liberates the substance that may in turn affect other sensitive bacteria.

Hadley (9), on the other hand, conceives of bacteriophage as a derivative, perhaps a filtrable form, of bacteria and related to the life cycles of bacteria. The bacteriophage in this instance stimulates the microscopically visible bacteria of the culture to pass into a submicroscopic filtrable stage. The outstanding feature of this theory is that it accounts more easily for the known resistant forms and the so-called "variants"

and secondary colonies that arise from lysed cultures.

Thus we see that a great deal of conjecture has to be dealt with in a treatment of this subject. The only working plans we have are based on those things that we can observe and demonstrate by use of cultural characteristics.

Characteristics of Bacteriophage

Briefly, we know the following facts, as summarized by Eaton and Bayne-Jones (10) from a Topley and Wilson publication:

1. Bacteriophage causes lysis of bacteria in cultures during early phases of bacterial growth. In cultures on agar, circular, clear, glassy areas of lysis are produced in the colonies or the edges of the colonies are "moth eaten" or indented. In broth cultures a partial or complete clearing of the originally turbid fluid occurs as a consequence of the dissolution of the bacterial cells.

2. As a result of the action of bacteriophage on a bacterial culture, variants of the bacterium arise. These variant strains may have increased or decreased virulence as compared with the culture from which they were derived. Many of the variants are completely resistant to the bacteriophage which lysed the sensitive parent culture.

3. Bacteriophage is filtrable through Berkefeld, Chamberland and other bacteria-retaining filters. The lytic principle can be separated by filtration from the intact bacterial cells.

4. Bacteriophage can be propagated in series indefinitely by transference of a small amount of fluid or filtrate from one lysed culture to another young, growing culture of susceptible bacteria.

5. Bacteriophage is active (in vitro) in high dilutions. Often one part of lytic filtrate to one billion parts of culture will bring about lysis.

6. Bacteriophage cannot be propagated on bacteria-free mediums, and

the lytic principle does not increase in association with old or dead bacteria, or bacterial products.

7. Young and actively growing cultures are lysed by bacteriophage. Old cultures, cultures not actively growing and cultures in which growth has been inhibited by antiseptics or other means are not dissolved.

8. Bacteriophages are usually specific for species or races of bacteria and have little or no effect on unrelated or dissimilar bacteria. Some lytic principles are strictly specific, others may affect related bacterial species or strains.

9. Changes in the ability of a specimen of bacteriophage to lyse or affect single species or groups of bacteria may be produced by serial propagation in association with susceptible bacteria. The activity of the lytic principle against a specific bacterium may often be increased, and its activity toward other strains may at the same time increase, remain unaffected or decrease.

10. The bacteriophage appears to be a particulate body. So-called races of bacteriophage have been estimated to have diameters of the order of from ten to fifty millimicrons.

11. Serologic studies indicate that bacteriophages have distinct antigenic properties.

12. The resistance of bacteriophage to heat and chemicals is less than that of bacterial spores but slightly greater than that of vegetative cells. It withstands aging for long periods.

The lytic principle is apparently found everywhere. It has been taken from the intestinal contents of man and animals, found in blood and in urine of convalescents, found in the soil, in river water, in sewage, in salt water close to shore, and everywhere that the waste products of the animal world are found. Hadley (11) has demonstrated that pyocyanus organisms may "carry" the lytic agent for hundreds of bacterial generations without giving any manifestation of

lytic action in the culture mass, so that its sudden appearance in some circumstances is more readily accounted for.

Limits of Bacteriophage in Use

From the beginning, d'Herelle has remained adamant in his belief in bacteriophage as a possible cureall for disease. However, certain considerations have been brought out which tend to limit its clinical possibilities.

First, the complexity of the bacteriophage mixtures is one cause of confused and contradictory publications. The usual material called bacteriophage is made by allowing lysis to proceed to completion in a young growing broth culture of some bacterium. This is then filtered through a Berkefeld, Seitz, or Mandler filter. This filtrate then contains (a) the lytic principle or bacteriophage, (b) products of the dissolved bacteria, (c) products of bacterial metabolism, (d) constituents of the culture medium. More specifically, the filtrate will consist of meat extractives and muscle proteins; amino acids, peptones and proteoses; nitrogenous organic bases; bacterial proteins and antigenic substances, and possibly the antiviral of Besredka. The question naturally arises, if this filtrate be injected into an animal or into man, and an effect is noted, to what will this effect be due? After all, are we discussing the results of bacteriophage therapy, or nonspecific protein therapy, or an ordinary vaccine?

Charnock (12) writes that the phenomenon of bacteriophagy which occurs under aerobic conditions, takes place during the period of division of the organism. If proliferation of the lysis is intimately linked with bacterial multiplication, we should expect a limitation as to phage formation according to the relationship which exists between it and the bacterium with which it is associated. Drs. Krueger and Northrup (13) have studied the kinetics of bacterium-

bacteriophage mixtures and concluded that the bacteriophage is formed within the bacterial cell and diffuses outward at such a rate that extracellular concentration and intracellular concentration of bacteriophage maintain to each other a constant mathematical ratio. These men have developed mathematical equations that accurately predict all the major events of this relationship, including the rate of bacterial growth, the rate of bacteriophage formation, time of lysis, and concentration necessary for bacteriostasis. Practically, these equations mean that a certain critical concentration of extracellular phage is essential for bacteriolysis, in about the same way that a critical environmental carbon dioxide concentration is necessary for death from carbon dioxide intoxication. Northrup and Krueger (14) have estimated that the phenomenon occurs only when the bacteriophagic particles reach a concentration of 110 inside the bacterial cell or a concentration of 1,200,000,000 per cc. in the environment of the cell. No therapeutic effects would be predictable, according to this line of reasoning, except under conditions in which local extrabacterial bacteriophage concentration can be raised to and maintained at this critical level. Such a critical extrabacterial concentration could hardly be expected in any tissue in which extracellular bacteriophage is denatured, bound, removed or diluted by such factors as circulation, lymph flow or urinary secretion, as will be pointed out later. The use of this therapy would thus be limited practically to such closed organs as the intestine and to well encapsulated pus cavities.

There is evidence to show that bacteriophage does not act *in vivo*; that is to say, it does not produce the same effects in the living organism that it does in the test tube. Investigators have found that certain body substances and fluids have an inhibitory effect on phage in

vitro, and it is assumed that these same effects or similar will occur *in vivo*. d'Herelle states (1): "When added to a bacterium-bacteriophage mixture, substances devoid of action upon the bacteria, have no effect on the phenomenon in general. Thus, the process is not modified by normal serum, ascitic fluid, or urine. Bile is unquestionably inhibitory." This statement was soon challenged. In studying specific antibacteriophage serums for the staphylococcus and the colon bacillus, Gratia and Jaumain (15) discovered a nonspecific transient inhibition of lysis by serum diluted 1:500. In contrast, they showed, too, permanent prevention of lysis by specific antibacteriophage serums.

In connection with phage therapy in cases of bacillary dysentery, Riding (16) tested effects of gastric secretion, intestinal mucus, and blood serum on the lytic activity of his dysentery bacteriophage. Gastric secretion did not affect lysis, while autoclaved 25% intestinal mucus, and 5, 10, and 20% serum prevented complete lysis. In a study of urinary infection Larkum (17) demonstrated that urine may be inhibitory to bacteriophage of colon bacilli, though some lysis can take place in the urinary bladder.

Applebaum and MacNeal (18) have shown that purulent exudate exerts a marked inhibitory influence on the lytic action of the antistaphylococcus bacteriophage, sufficient to explain the persistent survival of the bacteria in purulent collections within the body of a patient receiving treatment with potent bacteriophage. This inhibition is demonstrable even in dilutions as high as 1:1000. Undiluted citrated blood, undiluted defibrinated blood and diluted blood serum exercise an inhibitory influence on the antistaphylococcus bacteriophage, but there is considerable variation in behavior of different bacterial strains and apparently in behavior of different races of bacteriophage. Experiments with diluted serum, how-

ever, failed to reveal a clearly evident inhibition of the anti-colon bacillus bacteriophage.

That blood cells as well as serum may be inhibitory to bacteriophagy was shown by the work of Friedberger and Vallen (19), who found that a typhoid bacteriophage became inactive in the presence of unwashed red blood cells. Drs. Dresel and Lewis (20) also have pointed out that phage is without demonstrable bactericidal action in artificial tissue cultures. The plasma apparently inhibits both lytic action and proliferation. In such a lytically inactive bacteriophage-plasma mixture, the phage is not destroyed and can be recovered with but slight deterioration by appropriate plating methods.

Colvin (21), in a study of 55 patients, emphasizes the variation of serum, body fluid, race of bacteriophage and bacterial strain or species which introduces distinct differences in the amount of inhibition. He was not able to adapt a staphylococcal or a streptococcal phage to produce complete lysis in serum. He shows that repeated contact with serum may have a tendency to make an organism lysis-resistant and that consequently an adaptation to resist lysis develops. A study of the mechanisms of inhibi-

tion to lysis shows that serum delays multiplication of the bacteriophage but does not prevent specific fixation of the corpuscle. In the serum, the protein fraction is the main factor in inhibition of lysis, while in urine the crystalloid fraction inhibits.

These observations indicating the inhibitory action of body cells and fluids on bacteriophagy suggest that the process in the body is much modified as compared to in-vitro standards of lysis. This modification is in the direction of lessening the sterilizing capacity of the bacteriophage.

The practicability of this unusual phenomenon assumes a somewhat discouraging aspect when all the limiting factors such as the inhibitory action of certain mediums of use: the delicate and varying specificity of certain phages in reaction with certain strains of organisms: the adaptability of a phage to a specific organism, and the possibility that the phage phenomenon is but an induced invisible state, or produces this state in the life cycle of a bacterium, are reviewed. However, bacteriophage has been used with great apparent success in some therapy despite the many objections that have constantly been put forth against its use.

TABLE I

Inhibitory Action of Body Fluids (22)

Marked or Complete Inhibition with all Bacteriophages so far Investigated	Degree of Inhibition Varies with Different Bacteriophages and Different Animal Species
Whole blood	Pus
Undiluted serum	Urine
Bile	Ascitic fluid
Saliva (streptococcus only)	Cerebrospinal fluid
Autoclaved intestinal mucus (dysentery only)	

Treatment of Staphylococcal Infections

As might be expected, therapy has proven most successful in those places where the trouble can be treated locally and with the least interference of outside agents or body fluids that might tend to inhibit the beneficial

action of bacterial lysis. Thus we find many favorable reports on phage therapy in treatment of staphylococcal infections, such as furuncles, carbuncles, infected wounds of all sorts and osteomyelitis. (Continued on page 146)

May Program

Dr. Willis F. Manges

Professor of Roentgenology, Jefferson Medical College

Philadelphia, Pa.

Subject: X-Ray in Medicine.

May 19th, 1936

8:30 P. M.

YOUNGSTOWN CLUB

(Continued from page 144)

Dutton (23), working on staphylococcus septicemia, used filtrates that contained not only bacteriophage but also growth products and a high concentration of a bacterial protein. He states that the phage has proved to be of inestimable value in infections both local and systemic. In ten cases of staphylococcus septicemia in which two cc. of staphylococcus phage was given, recovery followed in nine out of the ten cases. Dutton remarks that systemic reactions seldom follow the subcutaneous or intravenous injections of staphylococcus phage, nor does any considerable local reaction develop. No evidence of anaphylaxis has ever been observed with intravenous or subcutaneous injections. The author insists on doses not over two cc. subcutaneously and one cc. intravenously. In his experience, no reactions attributable to peptone have ever occurred. Antistaphylococcus phage has been used by Combiesco and his associates (24) in the treatment of tonsillar abscesses with great success. As the results obtained by the authors with the staphylococcus phage were uniformly good no matter what the bacterial flora of the pus, they think that these results cannot be due to a specific action of the lytic principle or from its exclusive action. The action of fluids inoculated into the abscesses may consist of a stimulation of the defense elements of the organism. The stimulant may be the bacteriophage, the substances contained in the bacterial filtrates, the broth, the physiologic salt solution or other substances.

Walker (25) also speaks of the definite benefit to be derived from phage treatment of staphylococcal infections so situated that local dressings moistened with phage can be applied.

d'Herelle, working with Rakieten (26), showed that hemolytic staphylococci are particularly susceptible to bacteriophage and that resistant strains

of staphylococci are generally of the nonhemolytic type. These experiments are however concerned with conditions *in vitro* and do not give us very much of an idea as to the relative susceptibility *in vivo*.

Brulé and Sauvé (27) report that they have cured staphylococcus septicemia by injections of bacteriophage.

Thurman Rice (28) has had rather startling results in some instances. In treatment with phage, he was able to heal completely in three weeks a sinus and abscess of seven years' duration which hadn't been closed once in that time. He states that he has had excellent results with local application of phage filtrates to suppurative lesions due to the homologous organisms. Stock preparations seemed to be as efficacious as autogenous preparations and the dosage was not important, provided the filtrate was used in sufficient amount to give good contact as a wet dressing. Rice reports no bad results and no clinical evidence of the development of resistant strains that were more pathogenic than the original.

Larkum (29), at the Michigan Department of Health Laboratory, has prepared a polyvalent strain of staphylobacteriophage which has produced lysis of 110 out of 150 strains of staphylococci. He reports great success with this therapy over a five-year period. In 66 recorded cases, improvement in all but one case was noted when treatment was only given on two successive days with a subcutaneous injection of two cc. of the filtrate.

In the treatment of osteomyelitis, Dr. Albee (30) is very enthusiastic about the use of phage. He believes that the efficacy of the Orr closed treatment for osteomyelitis, in which the wound is closed without antiseptics and the dressings remain long undisturbed, is due to the spontaneous development of phage. If a spontaneous phage does not develop, Albee uses a prepared phage and reports

that with this method, the average healing time for a case of osteomyelitis is about six months. In this treatment especially, the use of antiseptics is warned against. All writers agree that antiseptics inhibit action of the phage.

MacNeal and Frisbee (31) in a detailed report of a study of staphylococcus bacteremia had a 50% mortality with the treatment by use of intravenous injections as well as subcutaneous and local application. They are very optimistic, however, in their outlook as to the possible benefits to be derived from this agent in the treatment of staphylococcus bacteremia.

It is only fair to suggest that in some of the clinical reports which show variations in successful treatment with phages that unless the clinician is using his own prepared and tested product, the commercial phage at his disposal may not be as effective as he supposes. Straub and Applebaum (32) made a study of some of the commercial bacteriophage products being offered for sale by various pharmaceutical companies and found quite a few of these products were only feebly lytic for the specified organism if at all, and some preparations contained preservatives in the form of antiseptics which have been shown to be unfavorable to the action of bacteriophage.

Streptococcic Treatment

Actively lytic streptococcus bacteriophages are much more difficult to prepare and the results of treatment have not been nearly as good as in staphylococcus infections. Alice Evans (33) has shown that antistreptococcus bacteriophage injected into mice inoculated with a minimal lethal dose of sensitive culture did not palliate the infection when the two doses were given simultaneously or when the bacteriophage and streptococci were incubated together previous to inoculation. Bacteriophage, injected intra-

venously into rabbits simultaneously with a dose of streptococcus which would kill the majority but not all of the control rabbits, failed to influence appreciably the mortality rate.

Colvin (34) also reports failure in an attempt to use in streptococcic lymphadenitis of guinea pigs, a bacteriophage of maximum virulence. No curative value was evidenced.

Genito-Urinary Tract

Again, in the treatment of urinary tract infections, the results have not been so good. Many strains of *B. Coli* are resistant to lysis.

In a report on 29 patients with colipyuria treated by Moltke (35), favorable results were secured in 17 cases. The phage was administered by injection into the bladder and intravenously, intramuscularly or subcutaneously. He ascribes recovery in these cases to local immunization.

According to Christiansen (36), the results of treatment of chronic pyelitis with bacteriophage are on the whole only fairly good. The situation might be improved, perhaps, if strain specific phage that causes rapid and complete lysis of the patient's bacteria were always used and due regard were paid to the acid reaction of the urine in colurias and the urine made alkaline before treatment.

Schultz (37) has spoken of the difficulties attendant on use of phage in this connection. Its usefulness is limited not only by the difficulty that attempts the procurement of suitable bacteriophages for individual cases but, to some extent, also by such obstacles as are offered by bacterial variation; by the difficulty of always contacting adequately the organisms within an infected tissue; loss of phage by drainage and its inactivation by the inflammatory exudate. Despite these potential obstacles, Schultz feels that in any infection for which a good bacteriophage can actually be provided, bacteriophage therapy always deserves a trial.

MacNeal (38) and his co-workers advise intravenous use of an asparagin preparation of colon bacteriophage in colon bacillus septicemia. In four of their cases the microbe present in the blood stream was found to be susceptible to lysis by their stock colon bacteriophage. The observations suggest that organisms of this group virulent enough to produce septicemia are in general more likely to prove susceptible to phage than those found in the intestine or in the urinary tract.

McCarthy and Ritter (39) have made a study of genito-urinary tract infections and they bring out a point well worth mentioning. It is important to make a complete urologic survey; there should be supplemental correction of the underlying pathology or anomaly as well as a search for the care of remote foci.

These authors are most enthusiastic in their report, having observed several spectacular recoveries. They state, "We assert without fear of contradiction that we have salvaged a number of lives by use of this agent, wherein no other method of which we have knowledge would have availed."

A typical case reported by these authors: J. S. B. referred for treatment of perineal fistula in 1931. Two years ago he was operated at the American Hospital in Paris for a prostatic abscess. The wound did not heal completely; a perineal fistula remained. An indwelling catheter was inserted for eight weeks. The fistula closed, but reopened fourteen months later and remained open. The urine was hazy with pus. A culture showed *B. Coli lactici*, which was susceptible to bacteriophage. Phage therapy was instituted and the treatment consisted of six instillations into the bladder and six subcutaneous injections. In ten days the patient was free of symptoms and negative to every known clinical and laboratory test. The perineal wound closed. Urine cultures were negative. The patient has since remained well.

In most of these case reports, how-

ever, there is a great deal of indefiniteness. The examinations do not follow the patients long enough; most reports end with the patient's exit from the hospital. It would naturally be hard to get follow-up data on such cases, but all this must be considered before we come to any definite conclusions.

Dysentery; Cholera; Typhoid

The disorders of the enteric group were the first to be studied in this connection and have given comparatively encouraging results.

d'Herelle (40) himself, since 1919 has been experimenting on patients affected with bacillary dysentery, giving each individual 2 cc. of a highly potent phage for dysentery bacilli. In all cases without exception, all of the morbid symptoms disappeared within a few hours, in from 4 to 20, according to the case, and the next day the patient was definitely convalescent. Since in this type of case, a potent phage, usually specific, can be isolated from the feces of the patient during the convalescent period but not during the severe illness nor for long during convalescence, d'Herelle believes this to be proof that the phage is responsible for the recovery. However, other workers claim that patients have recovered without phage in the intestinal contents and have also died despite its presence. Feemster (41), in observing 100 cases of ileocolitis, in which the Hiss-Y dysentery bacillus appeared to be the etiologic factor says that the detection in the stool of a bacteriophage active against the bacillus causing the outbreak of dysentery seems to be a supplemental and valuable procedure for determining the etiology of cases of diarrhea. Krenz (42) has found that the incidence of the bacteriophage in the stools of children with diarrhea of unestablished etiology is greater (45%) than in children with normal stools (16%).

Treatment of dysentery by use of phage is in wide use in the Soudan and South America (40, 12). In Brazil, the work is conducted by da

Costa Cruz at the Oswaldo Cruz Institute. The Brazilian Public Health Service has abandoned all other modes of treatment and sends dysentery bacteriophage over the infected areas of Brazil. But two failures are reported out of 10,000 cases.

In reports on the use of phage in treatment of typhoid fever, it is noted that shock often accompanies this method of treatment, intravenous and subcutaneous injections being more successful than the method of oral administration. The temporary relief may have thus been secured as a result of a protein shock reaction.

Ruchna and Melnik (43) have treated a series of 69 patients by this method and the mortality among those so treated was 5.8% as compared with the mortality among patients in the same epidemic not treated with the bacteriophage, of 7.5 to 8.5%.

d'Herelle (44) has reported rather startling effects in the treatment of Asiatic cholera. Appointed by the British government to take charge of a special mission to India, d'Herelle studied rather extensively the effects of phage in this connection. He succeeded in eradicating the disease and immunizing the population of large areas by transferring to the wells of the country merely from 30 to 40 cc. of the cultures of the phage which he easily obtained. In Rajiana, which has some 3000 inhabitants, there were 56 cases of cholera, from July 3 to

July 22. Treatment was begun July 21; there were four new cases July 23, but not a single case after that. In Lalpura, with 1,500 inhabitants, there were 39 cases from July 23 to July 26; July 28, there was just one new case and the epidemic was ended. As a result of this successful treatment, the Indian Government created a special laboratory for the preparation of the phage cultures for treatment of cholera and dysentery. Dr. Asheshov was selected as its director.

The most curious thing is the epidemiology of this disease as described by d'Herelle: The bacteria of the disease are imported into a town by a man suffering from the disease or one in the incubation period. From him, the cholera vibrios are distributed throughout the environment and the epidemic begins. The first few cases are usually fatal. Then a patient recovers and from this convalescent, a phage adapted to vibrio destruction is spread throughout the environment and recoveries become more frequent, the epidemic ending when the adapted phage becomes widely disseminated.

d'Herelle claims a mortality of 8% in the patients treated and of 62% in those not treated. According to Eaton and Bayne-Jones (45), these results are difficult to verify. Nevertheless, the epidemic of cholera in the Punjab region was stopped.

(Continued in next month's issue)

SOME REMARKS ON THE GONOCOCCUS BOUILLON FILTRATE

By HENRI SCHMID, M. D.

(Continued from our April issue)

In the establishment of cure antibodies must play the most important role. It is probable that they develop at the site of infection and that the nature of immunity is local rather than general.

Immunity, it is agreed, is a delicately balanced mechanism. It is slow to develop, retarded by systemic

complications, the use of alcohol, menstruation and sexual excitement. Pelouze has been preaching for a long time that the use of vaccines in the treatment of gonorrhoea, except under rare indications, is not only unnecessary, but harmful. He has definitely shown that the injudicious use of vaccine therapy makes for chronicity of the disease.

Other proteins than vaccine pro-

tein can influence unfavorably the clinical course of the disease. Howe, writing in the *British Journal of Venereal Diseases*, states that, in natives of West Africa suffering from acute gonorrhoea, arthralgia is sufficiently prominent to make it the initial symptom complained of in a large proportion of the cases. Yaws may be one of the factors which account for the excessive amount of joint pains in acute gonorrhoea and also for the remarkable frequency with which true gonococcal arthritis complicates the disease in all stages and in both sexes. For that reason Howe further states that Novarsenobillon is used routinely in addition to other ordinary treatment of gonorrhoea. And in this latitude, before the introduction of the Wasserman Reaction, when many cases of latent syphilis went unrecognized, it was good practice to administer mercury and potassium iodide in cases of stubborn chronic gonorrhoea. And again, whoever has had the occasion to treat a patient for acute gonorrhoea, while at the same time this patient was receiving elsewhere injections of pollen vaccine for a so-called "rose fever," will probably have noticed that in such a patient the disease lasted an unduly long time. We can only speculate as to the nature of such inter-reactions, but the notion of an heterophile antigen certainly fits into the picture.

Of vaccine therapy, Gay has this to say: "Vaccine therapy was not formulated and had not reached the consciousness of the practitioner until 1906. For something like six years following this period (1906-1912), as Irons has pointed out, the literature on the subject increased until it had reached formidable proportions. Since this time not only the literature but interest has waned, owing entirely to the fact that it has been realized that vaccine therapy has little to recommend it as a general procedure. Hektoen and Irons, in a consensus of opinions obtained from 1519 leading

practitioners in 1929, found that over 95% of them were no longer using vaccines in the treatment of infections. Their use had been recommended with varying emphasis in over 60 different infectious processes, but it has been realized that in very few of these are vaccines now considered as worthy of further trial."

There is no doubt that in localized infections such as in some complications of gonorrhoea, vaccines, judiciously used, produce at times good results. But, generally speaking, the fact that, under certain conditions, generalized infections do respond favorably to vaccines leads one to wonder whether the benefit derived from their use is not in reality attributable to non-specific protein therapy. The hope that Wright's work awakened, namely the cure of certain bacterial infections that are unaffected by serum therapy, has failed us. But it must be said that there is unquestionably a substance (opsonin) in the normal fluids that facilitates phagocytosis and that it is increased specifically by vaccination (tropin). The strongest element in natural resistance rests on the phagocytic cells and they are probably also the essential elements of defense in acquired immunity.

The benefit which may come and does come at times from the use of vaccines in chronic and acute infections is today thought to be non-specific and depends on the stimulation of the leucocytes rather than on an increase of specific opsonins or other antibodies. Such non-specific methods are exemplified by Bier's method of hyperemia and venous stasis, injection of leucocytic extracts, treatment of anthrax and other infections by pyocyanase, treatment of paresis by malarial inoculation, the use of colon bacilli vaccine in the treatment of typhoid fever and puerperal infections, the use of various serums, both of normal and of non-specifically immunized animals, of

peptones, albumin, dextrose, milk and colloidal metals.

Such are the modern teaching of immunology.

It is hoped that these remarks about the gonococcus and its behavior will help one to realize that this organism possesses a rather capricious, labile and probably variable antigen mosaic; and that it is hardly to be expected, under the present state of our knowledge, that any vaccine, filtrate or what not, prepared from this antigen will fit so well in the treatment of gonorrhoea as to be generally accepted.

The manufacturing biologist has, of necessity, no laboratory animal at his disposal on which to investigate the value of his biologicals for use in gonorrhoea. While his attempts to introduce valuable products to the medical profession are commendable we, in turn, who are the recipients of commercial periodicals sent to us gratis and who listen unwillingly to the pseudo-scientific talk of suave detail-men, should hesitate a bit before we ask our paying and trusting patients to act as human guinea-pigs for the one who benefits most from the sale and use of products the value of which is not fully determined.

Are You Going Away?

If so, perhaps you would be interested in combining business with pleasure. There comes to the Editor's desk, constantly, a number of publications from various medical centers, such as New York, Detroit, Cleveland, Chicago, and Kansas City. Each publication lists the medical clinics and activities for the forthcoming month. The Editor would be pleased to pass this information along to any one contemplating a visit to the above mentioned cities.

REVIVIFICATION

The ninth annual Postgraduate Day has passed on to take its place among its predecessors as a milestone in the history of our Society. This annual event, it is fair to say, is the outstanding medical achievement in Northeastern Ohio.

In retrospect, four factors stand out to impress us:

Firstly, the masterly statistical analyses and deductions therefrom of clinical material by Dr. Whipple. Also his impressive work in Surgery of the Pancreas.

Secondly, the careful and painstaking work of Dr. Palmer on metabolic disorders associated with dyspituitarism.

Thirdly, the originality of Dr. Barach in the study and uses of helium and oxygen in the treatment of respiratory disorders.

Fourthly, the masterly coördinative mind of Dr. Atchley, as typified in his afternoon paper on Peripheral Vascular Failure.

The opportunity which these meetings afford to meet the leaders in medical thought and analyse the traits that make them such, is inspiring.

We shall remember the Columbia group for long to come, and trust that their satisfaction in a job well done will be as great as has been our pleasure and privilege to have had them with us.

It may seem superfluous to comment upon the faultless arrangements for the meeting as carried out by the various committees. Yet each one of them put in long hours of work to make the meeting the success that it was, and to them is due our thanks.

Then, too, the firms and individuals who use our Bulletin as a vehicle for their advertising, by their exhibits, contributed an instructive and diverting touch to the meeting. Let us be mindful of our obligations to them and see to it that they are well repaid.

Analysis of Townsend Plan

Population of the United States	124,000,000
Eligible under Townsend Old Age Pension	50,000,000
Balance	74,000,000
Prohibited under Child Labor and Government Employment	60,000,000
Balance	14,000,000
Unemployed	13,999,998
Left to produce the Nation's goods	2

Apparently this leaves things up to you and me, and as I am not feeling so well, that pretty much puts the burden on you.

P-LEASE!

Lady (who brought her small son to the hospital for treatment): "It's his head, nurse. He's had it off and on ever since he was born."

Qualified.

Diner: "There's something wrong with these hot dogs."

Waiter: "Well, don't tell it to me; I'm only a waiter, not a veterinarian."—*Lorain (Ohio) Journal.*

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The probabilities are that no other class of offices are so frequented by those having something to sell as are the offices of the doctors, with the exception, of course, of the office of a purchasing agent. On the whole we are glad to be interviewed by the representatives of the firms and manufacturers who supply the profession and have brought to our intimate attention the new preparations and new forms of old remedies.

But there is one class of salesman who insinuate themselves into our offices to sell us a bargain. Perhaps it is neckties, suitings or what not; but whatever it is, the price is so much less. Do we ever stop to think just what it is we are buying, and by doing so, aiding and abetting? Goods are quite standardized as to quality and price. Like the automobile, you get just about what you pay for. Our local merchants are not cheats or deceivers. So then, if some itinerant salesman invades our offices with goods or merchandise at a price manifestly below the cost of a similar article in our local stores, the chances are ten to one that by purchasing from him you are aiding and abetting in the disposition of stolen goods.

The next time we are importuned not to forego the great opportunity to obtain something for almost nothing, let us do our mite toward frustrating a racket that costs our manufacturers, transportation companies and merchants, millions per year. Show the "gentleman" to the door, politely but firmly.

Out of His Line.

Father (admiring his recently born heir): "That fellow will be a great statesman one of these days."

Mother: "Oh, Charles dear, do you really think he will?"

Father: "Sure of it. Look how easily he wriggles out of everything."
 —*Toronto Globe.*

MEDICAL FACTS

By J. G. B.

In a recent article entitled "A Note on the Common Occurrence of Serious Involvement of the Heart in Hyperpiesia," Paul D. White says, "There has been a tendency in the postwar period to swing too far from the old extreme of great and general fear of high blood pressure to the other extreme of reassurance and relative neglect because we wish to avoid making our patients neurotic and particularly since we are still ignorant of the cause and the cure of hyperpiesia. We should, however, face the facts and take the middle course. . . . As the result of a discouraging experience with chronic and advanced hypertensive heart disease, I would urge the early discovery of hyperpiesia in patients and more intensive study and attempts at treatment at its onset."

According to Henry A. Christian, "A definite advance has been made in that a mercurial diuretic has been prepared by the Campbell Products, Inc., which is very satisfactorily effective when given by rectum in the form of a suppository. This is the highly complex organic mercury compound which is present in mercupurin, there combined with a xanthine substance. This obviates the necessity of intravenous or intramuscular dosage for mercurial diuretics, but still requires the preliminary days on ammonium chloride. The dose in suppository form is five times the dose for intravenous or intramuscular use. Experience shows that this treatment may be kept up for months with no bad effects."

Following extensive bacteriologic studies on appendicitis, Weinberg, of The Pasteur Institute, prepared three serums for the treatment of peritonitis secondary to appendicitis: (1) a polyvalent anaerobic serum, (2) a colon bacilli serum, and (3) a so-called "complementaire" serum directed

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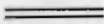
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against such organisms as streptococci, staphylococci and so forth. Professor Weinberg has given to the Mayo Clinic a supply of these serums for clinical trial, and for several years they have been used as an adjunct to the regular treatment of the peritonitis which follows appendicitis, with the hope of reducing the mortality from this disease.

Although experience to date is insufficient to warrant definite conclusions regarding the efficacy of these serums, they have been of definite benefit in a number of cases. Their use has not only reduced the mortality but the incidence of such complications as pelvic abscess, subphrenic abscess, and so forth is lessened, the amount and duration of drainage from the wound is reduced and also the period of necessary hospitalization is shortened.

As a problem in preventive medicine, coronary disease is now much larger and more important than is tuberculosis. It is second only to cancer. Denny thinks that little attention has been paid to the fact that the disease is rare in men with occupations requiring daily physical effort and most frequent in those with sedentary occupations, which suggests that physical inactivity predisposes to coronary disease. He suggests that "To prevent coronary disease a campaign of education is needed to teach the American people that *daily* exercise is one of the essentials of health."

Sixty-five hospitals in Massachusetts were selected as centers of special detailed study of serum treatment in pneumonia, and these hospitals served as depots from which serum was given to physicians cooperating in the study. Uniform records of nearly one thousand cases of lobar pneumonia were collected. The result of the campaign showed that when anti-pneumococcic serum was administered in sufficient amount within the first four days of the disease, there was a reduction of fifty-six per cent. in

May

the fatality rate of the Type I cases and of thirty-four per cent. in those cases due to a Type II infection.

To prevent nausea and vomiting following roentgenologic treatment W. C. Popp, Section on Therapeutic Radiology of Mayo Clinic, is now giving rectal administration of nembutal immediately after each treatment. He seems to be getting very good results.

CHRONIC ABSENTEES?

In advancing reasons for members to attend meetings read what Dr. Osler said in the International Clinics of 1910: "But after all, the killing vice of the young doctor is intellectual laziness. He may have worked hard at college, but the years of probation have been his ruin. Without specific subjects upon which to work, he gets the newspaper or novel habit, and fritters his energies upon useless literature. Habits of systematic reading are rare, and five or ten years from his license, as practice begins to grow, may find the young doctor knowing less than he did when he started and without fixed educational purposes in life. The man who knows it all and gets nothing from the Society reminds one of that little dried-up miniature of humanity, the prematurely senile infant, whose tabetic marasmus has added old age to infancy. Why should he go to the Society and hear Dr. Jones on the gastric relations of neurasthenia when he can get it all so much better in the work of Einhorn or Ewald? He is wearying of seeing appendices, and there are no more pelvic viscera for demonstration. It is a waste of time, he says, and he feels better at home, and perhaps that is the best place for a man who has reached this stage of intellectual stagnation."

SECRETARY'S REPORT

The fourth meeting of Council was held in Dr. Fuzy's office April 17, 1936, at 9 P. M.

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Dr. David Smeltzer presented the temporary plan of incorporating the Bulletin. After certain corrections were made he was authorized to proceed further with the proposal. In addition to this the regular routine duties were disposed of in the course of the evening.

The Public Health Committee has been doing a good job of putting on the campaign for diphtheria immunization. It requires a great deal of time and work to accomplish results in a campaign of this kind. Regulations can be had by communicating with Dr. E. Nagel, chairman of this committee.

The secretary received a letter from Dr. Wm. Skipp, Councillor of the sixth district of Ohio, announcing the next district meeting to be held in Ashland, Ohio, on the third Wednesday in May. All members of this district are invited to attend. He urges that the President, secretary, treasurer, chairman public relations committee, chairman economics committee and chairman of legislative committee be present at the mid-year organization conference of the Ohio State Medical Association at Columbus, Ohio.

Among the speakers at this meeting are Dr. Sidney McCurdy, Dr. O. J. Walker, and Dr. Walter King Stewart, members of Mahoning County Medical Society.

Secretary,

ROBERT B. POLING.

Kalak

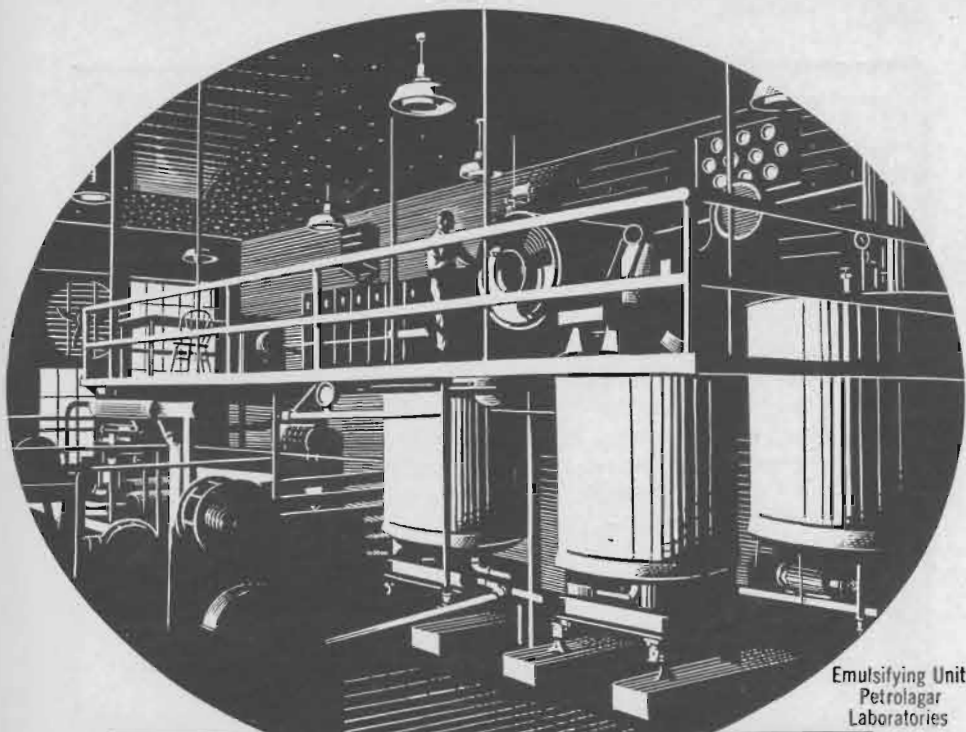
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