

with Antrenyl and infrequently with JB 323 (Piptal) in the decreasing order Antrenyl, Probanthine, Monodral, JB 323 (Piptal). JB 323 (Piptal) was the only substance in this study which had no urinary side effects.

The clinical results of these anticholinergic substances seem to depend on other factors besides their antisecretory effect.

REFERENCES

- 1a. Lorber, S. H. and Machella, T. E.: The effect of syntropan on the motor activities of the human gastrointestinal tract and on gastric acidity. *Gastroenterology* 12:57, 1949.
- b. Clark, B. B.: A comparison of the effect on gastric secretions of syntropan, demerol, and trasantine with atropine. *Gastroenterology* 9:454, 1947.
- 2a. Brown, H. S., Posey, E. L., Jr., and Gambill, E. E.: Studies of the effect of TEAC on gastric motor and secretory functions in patients with duodenal ulcer. *Gastroenterology* 10:837, 1948.
- b. Dodds, D. C., Ould, C. L. and Dailey, M. E.: The effect of tetraethylammonium chloride on gastric motility in man. *Gastroenterology* 10:1007, 1948.
- c. Zweig, M., Steigmann, F. and Meyer, K. A.: The effect of TEAC on gastric motility and on unstimulated and histamine-stimulated gastric secretion. *Gastroenterology* 11:200, 1948.
- d. Cayer, D., Little, J. M. and Yeagley, J.: The use of tetraethylammonium chloride in the treatment of patients with peptic ulcer. *Gastroenterology* 12:219, 1949.
- e. Neligh, R. B., Holt, J. F., Lyons, R. H., Hoobler, S. W. and Moe, G. K.: Effects of TEAC on the human gastrointestinal tract. *Gastroenterology* 12:275, 1949.
- f. MacDonald, I. R. and Smith, A. N.: Effect of tetraethylammonium bromide on gastric secretion and motility. *Brit. M. J.* 2:620, 1949.
3. Kirsner, J. B. and Palmer, W. L.: Newer gastric anti-secretory compounds. *J.A.M.A.* 151:798, 1953.
4. Hambourger, W. E., Cook, D. L., Winbury, M. M. and Freese, L. T. B.: Pharmacology of B-diethylamino ethyl xanthene-9-carboxylate methobromide (banthine) and chloride. *J. Pharmacol. and Exper. Therap.* 99:245, 1950.
5. Ferrer, J. M.: The effect of tetraethylammonium chloride on gastric secretion and acidity in peptic ulcer. *Surg., Gynec. and Obst.* 87:76, 1948.
6. Paton, W. D. M. and Zaimis, E. J.: The pharmacological actions of polymethylene bistrimethyl-ammonium salts. *Nature, London* 162:810, 1948.
7. Graham, A. J. P.: Toxic effects in animals and man after tetraethylammonium bromide, *Brit. M. J.* 2:321, 1950.
- 8a. McHardy, G. and Browne, D. C.: Clinical Appraisal of gastrointestinal antispasmodics. *South. Med. J.* 45:1139, 1952.
- b. See 3.
- 9a. Longino, F. H., Grimson, K. S., Chittum, J. R. and Metcalf, B. H.: An orally effective quaternary amine, banthine, capable of reducing gastric motility and secretions. *Gastroenterology* 14:301, 1950.
- b. Benjamin, F. B., Rosiere, C. E. and Grossman, M. I.: A comparison of the effectiveness of banthine and atropine in depressing gastric acid secretions in man and dog. *Gastroenterology* 15:727, 1950.
- c. Walters, R. L., Morgan, J. A. and Beal, J. M.: Effects of B-diethyl-amino-ethyl xanthine-9-carboxylate methobromide (banthine) on human gastro-intestinal functions. *Proc. Soc. Exper. Biol. and Med.* 74:526, 1950.
- d. Grimson, K. S., Lyons, C. K. and Reeves, R. J.: Clinical trial of banthine in 100 patients with peptic ulcers. *J. A. M. A.* 143: 873, 1950.
10. Kirsner, J. B., Palmer, W. L., Levin, E. and Klotz, A. P.: Gastric antacid and anti-secretory drugs: A survey based primarily on their effects upon gastric secretion in man. *An. Int. Med.* 35:785, 1951.
- 11a. Margolin, S., Doyle, M., Giblin, J., Makovsky, A., Spoerlein, M. T., Stephens, I., Berchtold, H., Belloff, G. and Tislow, R.: Pharmacological properties of a new parasympathetic blocking agent, N,N Dimethyl 4-piperidylidene 1, 1 Diphenylmethane Methyl Sulfate (Prantal), *Proc. Soc. Exper. Biol. & Med.* 78:576, 1951.
- b. Texter, E., Jr., Baylin, G. J., Legerton, C. W. and Ruffin, J. M.: Effects of a new cholinergic blocking agent (SKF-1637) on gastric motor and secretory activity. *Am. J. Med. Sci.* 224:612, 1952.
- c. Bolt, R. J., Bratt, H. and Pollard, M. H.: Action of a new synthetic antispasmodic in patients with gastrointestinal complaints. *Gastroenterology* 24:204, 1953.
- d. Rogers, M. P. and Gray, C. L.: A new anti-ulcer drug: A clinical and radiological evaluation. *Am. J. Digest. Dis.* 19:180, 1952.
- e. Charles, C. H.: Further experience with anticholinergic Drugs: A clinical appraisal in 201 patients. *Cleveland Clin. Q.* 20:415-23, 1953.
- f. Kirsner, J. B., Levin, E. and Palmer, W. L.: Pamine bromide: Gastric antisecretory effects and therapeutic usefulness in peptic ulcer and other gastro-intestinal disorders. *Gastroenterology* 26:852, 1954.
12. Legerton, C. W., Texter, E. C., Jr., and Ruffin, J. M.: The mechanism of relief of pain in peptic ulcer by banthine. *South. Med. J.* 45:310, 1952.

THE USE OF CITRUS FLAVONOIDS IN INFECTIONS. II.

MORTON S. BISKIND, M.D., Westport, Connecticut AND WILLIAM CODA MARTIN, M.D., New York, N. Y.

THAT DISTURBANCES of capillary function accompany the inflammatory process, has long been known. The physiologic and morphologic changes in the vessels that accompany this phenomenon were described in Krogh's classic Silliman lectures (9) of 1922:

"In inflammation the circulatory phenomena are generally very conspicuous and by a large school of pathologists

they are regarded as the primary and essential symptoms to which all others can and should be referred. . . . In my opinion, the vascular reactions in typical inflammation are, in the main, of a secondary character, though . . . they form, nevertheless, an element of prime importance in the complicated inflammatory processes. . . .

"It may very well be worth while to study the vascular reactions during inflammation with the object in view of getting them under control, of restraining them at the points

where they become harmful and of helping them on where they are beneficial."

In inflammatory reactions caused by infection, there is invariably involvement of the capillary circulation. The changes that occur in the capillaries at the site of inflammatory lesions were never better described than in some of the older textbooks of physiology (e.g., 21) and pathology (e.g., 7). Briefly, there is first dilatation of the vessels, with increased blood flow, followed by a slowing of the axial stream and collection of leukocytes along the capillary wall; the leukocytes may then emigrate through the wall by diapedesis. There is simultaneously transudation of protein-containing fluid through the capillary wall, with production of localized edema, and, in some infections, rupture of the capillary intercellular cement occurs with release of erythrocytes, producing "hemorrhagic inflammation." This phenomenon is not restricted to bacterial infections, nor even to the site of invasion of the infective agent. Sokoloff (16) has recently reviewed changes in capillary permeability and fragility which are known to take place in many viral infections and which often are not restricted to sites of invasion or localization, but occur throughout the body.

In a preliminary note (5), we have reported our initial findings on the remarkable ameliorative effects of the water-soluble citrus bioflavonoid complex in acute respiratory infections. Rhinitis, pharyngitis, influenza, tonsillitis and the like usually subsided completely in from 8 to 48 hours. Further observations confirm these findings and indicate that the beneficial effects of the flavonoids are not confined to respiratory infections or solely to viral diseases. Our results strongly suggested that the flavonoids operate in the infections, at least in part, by restoring normal capillary integrity, a function of this group of compounds originally demonstrated by Armentano, Szent-Györgyi and their associates (1) in 1936. While our own observations were entirely empirical in basis, Krogh's suggestion of more than thirty years ago has proved to be a valuable one indeed.

In addition to the 23 cases of respiratory infections treated with citrus flavonoids, which were the subject of our preliminary report, we have investigated the effects of flavonoid therapy* in an additional 46 cases, or a total of 69. Our subsequent observations have fully confirmed our conclusion that these substances are of inestimable value in the treatment of certain infections. In addition to our series of cases, Sokoloff (16) has reported five cases of influenza, verified as caused by influenza virus A, in which recovery occurred by crisis within 48 hours, under large dosage therapy with the citrus flavonoids.

Following are brief additional descriptions of typical cases:

*The preparation used in this study was C.V.P.®, a mixture of equal parts of whole water soluble natural citrus flavonoid complex, and ascorbic acid. These citrus flavonoids, similar to, but not identical with, the original preparation of Szent-Györgyi, which he designated vitamin "P", have been described by Sokoloff, Eddy and Redd (17). The commercial preparation, kindly supplied by the U. S. Vitamin Corporation, contains in each capsule 100 mg. each of flavonoids and ascorbic acid. Throughout this paper, except when otherwise specifically stated, dosage refers to the flavonoid component (100 mg.=1 capsule).

A woman, age 49, developed an acute membranous tonsillitis and pharyngitis, with a temperature of 101 F. She was given 200 mg. of flavonoids every 3 hours (1.8 Gm. per day). In 48 hours the temperature was normal, injection and swelling were gone and the membranous coatings were found to be peeling off without bleeding and with normal appearing mucosa underneath. The patient could now swallow without discomfort and had little residual malaise (after a total dosage in 48 hours of 3.2 Gm.).

Another patient, age 55, a telephone operator, was seen 48 hours after development of a severe rhinitis. There was no fever. This patient had a history of almost invariable chest involvement following previous attacks of rhinitis and subsequent development of asthma. On several occasions the latter required hospitalization for 2 to 3 weeks. She was given 200 mg. of flavonoids 3 times a day and was completely free of symptoms in 36 hours. In contrast to previous experience, the patient was able to continue at her work. As she expressed it, "For the first time in my life the cold cleared up like magic."

In another patient, female, age 43, with acute laryngitis and pharyngitis, there was complete subsidence of symptoms in less than 72 hours on a flavonoid dosage of 200 mg. 3 times a day.

A woman, age 48, developed influenza while taking soluble citrus flavonoids 200 mg. per day, as a maintenance dose against increased capillary fragility. She had pharyngitis, rhinitis, sinusitis, severe malaise and a temperature of 99.7 F. The flavonoid dosage was increased to 800 mg. per day (2 capsules 4 times a day). Two hours after the first dose of 200 mg. there was noticeable thickening of nasal mucus. The temperature was normal in 14 hours (after 600 mg.) and all signs and symptoms, local and systemic, had subsided except for persistence of some thickened mucus in the nasal passages. There was a marked sense of relief and well-being the next day, on which the patient remarked spontaneously. Flavonoid therapy was continued, 600 mg. a day, for another week, until nasal secretions were normal. Previous experience of this patient with respiratory infections was that while they occurred rarely, when they did the course was extremely severe and residual symptoms were very persistent, lasting usually for several weeks. An interesting observation in this case is that a long-standing rheumatoid arthritis of the hip cleared up completely during the flavonoid therapy (this response to flavonoids in certain cases has been reported by Sokoloff and Eddy (18)).

A male diabetic, age 41, developed rhinitis while taking 600 mg. of flavonoids per day for therapy of retinitis. The same dosage was continued; in contrast to his usual experience, there was rapid thickening of nasal mucus and this infection lasted only 3 days and was mild in character. Respiratory infections in this patient had previously invariably lasted considerably longer and were usually severe.

A man, age 43, developed a severe rhinitis with copious watery secretion. On a dosage of 600 mg. of flavonoids the first day, and 900 mg. per day on the two following days, there was complete subsidence of all symptoms in approximately 52 hours. In this case,

excess nasal secretion subsided without going through the phase of thickening. There were no residual complications although previous experience of this patient had been that attacks of rhinitis were invariably followed by persistent frontal sinusitis.

In a few patients discontinuance of therapy as soon as the respiratory symptoms subsided was followed by recrudescence of the infection which, however, again responded to flavonoid therapy. It seems advisable therefore to continue flavonoid therapy for at least a few days after the infection has subsided, and especially when minor signs, such as thickened mucus, persist.

While the large majority of patients thus far studied have responded dramatically to the flavonoids, in three of our more recent cases, all severe respiratory infections with bronchial involvement, the flavonoids failed to arrest the infection in the usual time, but appeared to modify considerably the course of the infection as compared to previous similar attacks in the same patients. In the case of a man, age 48, who had been accustomed to a yearly bout of influenza for more than ten years, fever had usually risen to 101.5 F. for three or four days, and after subsidence of the infection there had always been asthenia and persistent cough for from two to four or five weeks. In his current attack, flavonoid therapy, 200 mg. 4 times a day, was administered; the temperature rose only to 99.5 F. and was normal in 24 hours; rhinitis subsided completely in 5 days and the cough had disappeared in 10 days. There was noticeably less asthenia than in previous attacks. In this patient too, as in one of those previously mentioned, a long-standing arthritis of one shoulder cleared up almost completely, leaving no pain and only slight limitation of motion. About two months later, this patient again developed a severe rhinitis with copious watery secretion. Two doses of flavonoids, 200 mg. each, were administered during the late afternoon and evening. By morning nasal mucus was extremely thick and breathing was difficult. With a single additional dose of 200 mg., the thickened mucus had almost disappeared an hour later, and about 20 hours after the initial symptoms began, the attack had subsided completely.

In our subsequent experience, in only one further case (in addition to the two failures previously reported) was there an apparent failure of flavonoid therapy. This was in a severe respiratory infection with bronchial involvement. The patient discontinued therapy after three days when the infection did not subside. There is no way of estimating in this case whether or not the flavonoids modified the course of the infection.

Trial of the flavonoid preparation in acute bursitis has led, in the few cases we have so far investigated, to such rapid and complete relief as to warrant mentioning this experience also. One case is illustrative: A man, age 38, had severe subpatellar bursitis. There was extensive local swelling, local heat, extreme tenderness, severe pain and limitation of motion. On flavonoids 200 mg. 3 times a day, there was noticeable diminution in swelling and pain in 24 hours, and in 72 hours the lesion had subsided almost completely, leaving only slight local tenderness.

DOSAGE

The dosages of the flavonoid-ascorbic acid mixture we have used in the infections have varied from 3 to 16 capsules (300 mg. to 1.6 Gm. each of flavonoids and ascorbic acid) a day, in divided doses. Optimum dosage has not as yet been worked out, but at present our dosage range is usually from 6 to 12 capsules a day, depending on the severity of the infection. Except for occasional central nervous system stimulation (and rare insomnia) on the higher amounts, which subside immediately on reduction of dosage, no ill effects have been observed. Sokoloff (16) has used even higher dosages (up to 24 capsules in 24 hours) in influenza, without apparent ill effect.

DISCUSSION

In our preliminary report, as already noted, we suggested that the flavonoid preparation operates in the infections by restoring normal capillary permeability. It is presumed that this aids recovery by preventing further penetration through the capillary wall of the large molecular proteins (6, 20), making up the attacking virus, or of other large molecular aggregates, such as bacterial polysaccharides.** It is well known that in early stages of increased capillary permeability, large molecules, normally retained, may penetrate through the capillary wall. And it has been demonstrated that this can be prevented by the administration of the citrus flavonoids (17-19). Menkin has isolated a substance from inflammatory tissue ("leukotaxine"), that damages the capillary wall. In animal experiments, Sokoloff and Eddy (18) have demonstrated that the citrus flavonoids can prevent the capillary damage produced by Menkin's leukotaxine, and that produced by bacterial polysaccharides. They have also shown that the soluble citrus flavonoid complex is much more effective in this respect, on an equal weight basis, than the insoluble flavonoids, such as rutin and hesperidin.

It appears therefore that in infections, a vicious cycle of capillary damage may be induced. Initially increased capillary permeability, from lack of suitable local tissue nutrition, from anoxia, or from chemical or physical damage, may permit penetration of large molecular infective agents or their growth products through the capillary wall. The infective agents, or their products, further increase capillary permeability,

**It should be kept in mind that certain relatively small molecular toxic chemical compounds may undoubtedly penetrate capillaries of normal permeability. This is especially important in view of the pervasive exposure to the chlorinated cyclic hydrocarbons (DDT, lindane, chlordane, and the like) which can induce chemical rhinitis, pharyngitis and interstitial pneumonitis with mononuclear infiltration. It is important that these conditions be differentiated from actual infections (4). Similarly, the organic phosphorus insecticides (e.g., parathion, TEPP, malathion) can induce copious rhinorrhea, through inhibition of cholinesterase and release of excess acetylcholine (3). These conditions can hardly be expected to respond to the flavonoids.

Reservation must also be made with regard to current concepts as to the alleged invariably infective nature of poliomyelitis (recently the subject of a monumental review by Scobey (15)), and that of many of the cases diagnosed as "virus hepatitis" (4). Obviously, however, there may nevertheless be increased capillary permeability and fragility in all these conditions, regardless of etiology, and the capillary damage should of course be treated.

and when inflammation occurs, local tissue products also take part in this process. The end result may be extensive capillary damage throughout the body, and in fact, precisely this latter phenomenon is known to occur.

Sokoloff (16) has reviewed the extensive evidence from the clinical literature showing that many viral infections are complicated by either local or widespread severe damage to the capillary walls with increased permeability and increased fragility. This has been found to occur for instance in such diverse conditions as poliomyelitis, infectious hepatitis, rheumatoid arthritis, measles, yellow fever, the common cold, influenza, smallpox, encephalomyelitis, mumps and rabies. Thus not only does the "capillary syndrome" provide a theoretical basis for better understanding and further investigation of the processes of invasion, tissue response and resolution in a variety of infections, but recognition of the role played by changes in capillary permeability and fragility provides a new and dramatically effective means of therapy. In the common cold, for instance, it is well recognized that factors which induce local ischemia and resultant anoxia (e.g. chilling, psychogenic disturbances, etc.), impaired local nutrition, irritants and the like, all of which are known to increase capillary permeability, may enhance susceptibility to the disease.

It is of great interest that citrus juices have a long tradition of usefulness in folklore against respiratory infections. Of course, the possible dosage of soluble flavonoids in the quantities of juice usually imbibed for this purpose, must be quite small in comparison with that which we have found to be effective. Nevertheless, some persons appear to respond to dosages as low as 200 or 300 mg. of flavonoids per day, and no doubt this explains the long persistence of this tradition. Of equal interest is the fact that among the esoteric remedies employed by certain African tribes, is one "for influenza and some fevers," which consists of "an hourly dose of salted liquid from boiled red peppers" (10). As Szent-Györgyi and his associates (1) demonstrated years ago, the pepper plant is a rich source of the vitamin P flavones.

Large dosages of ascorbic acid alone have been reported also to have ameliorative effects in respiratory and other infections (8, 11). These dosages (often given parenterally) are ordinarily very much larger than that in the amounts of flavonoid-ascorbic acid mixture we have used, and in our experience have rarely given responses comparable to those reported in this paper. It is of interest that secondary effects of ascorbic acid, such as hypoglycemic reactions occasionally observed, have not occurred in this series when the flavonoids were administered simultaneously. In the earliest investigations on the flavonoids, synergism between vitamins P and C on capillary permeability was observed, and it appears probable that other interactions of these vitamins also occur. Their occurrence together both in plants and in animal tissues likely reflects this phenomenon. In our preliminary report we pointed out, that although the effects on capillary permeability*** appear to be the most likely

***The role played by changes in permeability of lymphatic vessels is a subject which also requires elucidation. The uptake of antigens and of virus particles by the lymphatic

circulation and the participation of the regional lymph nodes in the resultant immune phenomena were studied ingeniously twenty years ago by McMaster and Hudaek (13). In their studies the lymphatic vessels were necessarily opened at one or more points, and the extremely difficult task of assessing permeability of intact lymphatics has yet to be done.

explanation of the remarkable ameliorative effects of the flavonoids in infections, the possibility of other anti-infective properties was not excluded. While preliminary observations made by us indicate that the flavonoids can reduce the severity of local bacterial infection and hasten healing in animal and man, Dr. Boris Sokoloff, in a personal communication, has informed us that the citrus flavonoids have only a slight antibiotic effect in vitro. With respect to viruses, however, a recent report by McKeen (12) provides a basis for further investigation: This observer has shown that the juice of the pepper plant (*capsicum frutescens*) greatly diminishes the infectivity of cucumber mosaic virus, ringspot virus and tobacco etch virus on a variety of plants susceptible to these infective agents. While McKeen does not indicate the nature of the active substance in pepper juice, as already mentioned this plant is rich in flavonoids. Other authors have discussed at length evidence relating to the roles of the flavonoids in plant metabolism, in detoxication, oxidation-reduction mechanisms, maintenance of normal cellular membranes and the like (18).

SUMMARY

In 69 cases of acute respiratory infections (of which 23 have previously been reported), including the common cold, acute follicular tonsillitis and influenza, oral therapy with the whole water soluble citrus flavonoid complex (vitamin "P" complex) led to rapid subsidence of the infection usually in from 8 to 48 hours, occasionally somewhat longer. There were only 3 failures, and 3 further cases in which the course of the disease was apparently ameliorated but not immediately terminated. Preliminary observations suggest dramatic usefulness also in bursitis and in certain other types of infection.

The effectiveness of the flavonoids in infections is thought to be related to their ability to restore to normal impaired capillary permeability and fragility, a disturbance common to a large variety of infections.

The observations reported in this paper, assessed together with the widespread occurrence of the flavonoids in plant and animal tissues, suggest a much more fundamental role for these biologic substances than has hitherto been appreciated.

REFERENCES

1. Armentano, L., Szent-Györgyi, A. et al: Über den Einfluss von Substanzen der Flavongruppe auf die Permeabilität der Kapillaren; Vitamin P, Deutsche med. Wchenschr. 62:1325, 1936.
2. Bicknell, F., and Prescott, F.: The Vitamins in Medicine, 3rd Edition, New York: Grune & Stratton, 1953.
3. Biskind, M. S.: The Technic of Nutritional Therapy Am. J. Dig. Dis. 20:57, March, 1953.
4. Biskind, M. S.: Public Health Aspects of the New Insecticides. Am. J. Dig. Dis. 20:331, November, 1953.
5. Biskind, M. S., and Martin, W. C.: The Use of Citrus

phatic circulation and the participation of the regional lymph nodes in the resultant immune phenomena were studied ingeniously twenty years ago by McMaster and Hudaek (13). In their studies the lymphatic vessels were necessarily opened at one or more points, and the extremely difficult task of assessing permeability of intact lymphatics has yet to be done.

- Flavonoids in Respiratory Infections. *Am. J. Dig. Dis.* 21:177, July, 1954.
6. Editorial: A Crystalline Protein Having the Properties of a Virus. *J. A. M. A.* 105:371, August 3, 1935.
 7. Karsner, H. T.: *Human Pathology*, Phila.: J. B. Lippincott, 1926.
 8. Klenner, F. R.: The Use of Vitamin C as an Antibiotic. *J. Applied Nutr.* 6:274, 1953.
 9. Krogh, August: *The Anatomy and Physiology of Capillaries*, New Haven: Yale University Press, 1922.
 10. Lake, Alexander: *Hunter's Choice*, N. Y.: Doubleday, 1954.
 11. McCormick, W. J.: Vitamin C in the Prophylaxis and Therapy of Infectious Diseases, *Arch. Pediat.* 68:1, January, 1951.
 12. McKeen, C. D.: Inhibition of Virus Infections of Certain Plants by Extracts from *Capsicum frutescens* L., *Science* 120:229, Aug. 6, 1954.
 13. McMaster, P. D.: Conditions in the Skin Influencing Interstitial Fluid Movement, Lymph Formation and Lymph Flow, *Ann. N. Y. Acad. Sc.* 46:743, Sept. 16, 1946; McMaster, P. D., and Hudaek, S. S.: *J. Exper. Med.* 61:783, 1935.
 14. Scarborough, H.: *Vitamin P, Vitamins & Hormones* 7:1, 1949.
 15. Scobey, R. H.: Is Human Poliomyelitis Caused by an Exogenous Virus? *Arch. Ped.* 71:111, April, 139, May, 1954.
 16. Sokoloff, B.: The Capillary Syndrome in Viral Infections, Treatment with Citrus Flavonoids. *Am. J. Dig. Dis.* 22: 7, Jan., 1955.
 17. Sokoloff, B., Eddy, W. H., and Redd, J. B.: The Biological Activity of a Flavonoid (Vitamin "P") Compound. *J. Clin. Invest.* 30:395, April, 1951.
 18. Sokoloff, B., and Eddy, W. H.: Bio-Flavonoids in Capillary Fragility, Capillary Fragility and Stress, Monograph No. 3, Florida Southern College, 1952.
 19. Sokoloff, B. and Eddy, W. H.: Bio-Flavonoids in Radiation Therapy, *ibid.*, 1952.
 20. Stanley, W. M.: Isolation of a Crystalline Protein Possessing the Properties of Tobacco-Mosaic Virus. *Science* 81:644, June 28, 1935.
 21. Starling, E. H.: *Principles of Human Physiology*, 4th Edition, Phila.: Lea & Febiger, 1926.

DIARRHEAL DISEASES: A PLAN FOR THEIR PREVENTION AND CONTROL

WILLIAM Z. FRADKIN, A. B., M. D., Brooklyn, New York.

NO ONE complaint or group of complaints has caused so much suffering, to so many millions of people, for so many centuries, as the complaint of diarrhea. This symptom has been a constant and embarrassing companion of man in civil as well as military life. Although definite progress has been made in etiology and epidemiology, there is sufficient evidence to indicate that diarrheal diseases in general, are increasing.

Statistics on the true incidence of diarrheal disorders are lacking. The wide prevalence of these diseases may be surmised by the astounding fact that the sales of intestinal adsorbents for one year amounts to millions of dollars! About four million prescriptions for intestinal adsorbents are filled each year (1). Another fact is the unusual and increasing amount of toilet tissue used in the United States (2). For example, in 1946 four hundred thousand tons of toilet tissue were sold. In 1951 the sales increased to 588,000 tons—a staggering figure! In other words, about two and one-half rolls of toilet tissue were used on the average by each person per week. Although this figure does not represent its use exclusively for sanitation purposes, it is primarily used as a toilet tissue and gives some indication of the prevalence of all types of diarrheal disorders. Interestingly enough, this increase coincides with a corresponding rise in the number of enteric infections recorded for that period in the various Public Health reports (3).

ETIOLOGY

It is estimated that about ten percent of our popu-

Submitted Aug. 2, 1954.

lation are carriers of *Entamoeba histolytica* (4). Diarrhea is the chief complaint of fifty percent of these carriers. An unknown percentage suffer with or harbor the other recognized intestinal pathogens, such as *Giardia lamblia*, *Balantidium coli*, shigella, staphylococci, salmonella, and other bacterial enteric infections. Add to these the viral causes, chronic ulcerative colitis and regional enteritis of undetermined etiology, psychic, allergic, glandular, neoplastic, and the diarrheas caused by heavy metals, chemicals, radiation, nutrient deficiencies, intestinal worms such as *schistosoma mansoni* and *japonicum*, *strongyloides*, and one will realize that an enormous number of people are involved. A conservative estimate would be about sixteen million inhabitants of our country.

FOOD SERVICE

The possibility for accidental contamination of food resulting in diarrhea has increased enormously through the years. There are about 310,000 public eating places in the United States, where approximately 53,500,000 meals are served daily to persons outside their homes (5). The consumption of sandwiches in this country has increased 215%, and salads 110%. Mass food preparation and service involve millions of foodhandlers. Among them are careless cooks, waiters and dishwashers who know little about personal or environmental hygiene. Neither are they aware of their position as important links between health and disease, carrier states and epidemics.

The supervision of so complex a structure is difficult, to say the least. Educational campaigns have been inadequate. The average layman is not suffi-