Pectin and its therapeutic use: with special reference to the treatment of diarrhea in infants and children

Ralph L. Oppen
University of Nebraska Medical Center

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PECTIN, AND ITS THERAPEUTIC USES,
WITH SPECIAL REFERENCE TO THE TREATMENT OF DIARRHEA
IN INFANTS AND CHILDREN

SENIOR THESIS

BY

RALPH L. OPPEN

* * *

PRESENTED

to the

UNIVERSITY OF NEBRASKA

COLLEGE OF MEDICINE

OMAHA 1940
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INTRODUCTION

The treatment of the diarrheas of infancy and childhood is a matter in which all general practitioners and pediatricians are vitally interested. This widely prevalent affliction is one which can vary in severity and duration. In the past, particularly, it has carried a heavy toll of death. In 1928 a physician in Germany was influenced by a number of surprising incidents brought to his attention, of the use of the apple in treatment of diarrhea. In reviewing the literature we find that the apple was used in folk medicine, more than any other fruit. The story of the development and chemistry of pectin begins, as far as the physician is concerned, with the Raw Apple Treatment for diarrhea. Now, we find advancement in this form of treatment, in Pectin-Agar. Also new possibilities for the use of Pectin in other fields are claimed by many others.

Pectin is new and it is very gratifying to observe that the new concepts of this condition (diarrhea) have led to a more rational treatment and consequently to infinitely better results.

Because of the dramatic development of this new drug and its current interest to the medical profession,
I will review its history, and the present concepts and uses, with a summary of the results and rationale for this new treatment.
Among the substances found in plant life and of which little is generally known is a group called pectic substances. These substances are found in the cell wall of plant tissue and are grouped into three general classes termed protopectin, pectin and pectic acid.

Braconnot, a French worker, is credited as being the first to extract pectin materials from plants. This work was published in 1825, a little over one hundred years ago. He extracted what he termed pectin acid from the roots of several vegetables and from the leaves and stems of plants and trees. Braconnot took the name pectin from the Greek word "pi eta chi tau iota sigma" (Greek Letters, Ed.).

He described and named pectic acid and suggested the first medicinal uses for it, and his first usage was in the formation of artificial jellies flavored with rosewater to make delicacies especially attractive to convalescent persons. Having observed the formation of insoluble compounds of pectic acid with lead and other heavy metals, he suggested its use as an antidote in case of heavy metal poisoning.

PECTIN, WHAT IS IT?

The interesting properties of pectin which Braconnot described have continued to fascinate chemists. The chem-

istry of pectin has therefore been the subject of extensive research during the last 100 years, but the complex colloidal nature of the substance has permitted only the slow progress. The many erroneous conceptions which have been in vogue need not be discussed here. The modern viewpoint really started with Fellenberg about 1915, who proved that the pectin molecule contained several acid groups some of which were neutralized by methyl alcohol in ester linkage. The pectinous material in fruits and vegetables were shown by him to be the source of methyl alcohol found in wines and spirits made therefrom. Shortly afterwards Ehrlich showed pectin to be an anhydride of a tetra-galacturonic acid ester with methoxyl and acetyl groups. This pectin galacturonic acid gives characteristic reactions (i.e., brick red color of the naptho-resorcinol with lead acetate.) This proves that the organic acid present in pectin is galacturonic acid.

Galacturonic acid is related to galactose in the same manner as glucuronic acid is related to glucose, and the two substances are isomeric. The following formulas show these relationships and also illustrate two different methods of indicating the pyranose configuration of the galacturonic acid anhydride units, present in the pectin molecule.
Galactose  Galacturonic Acid  Galacturonic Acid Anhydride
Unit of the Pectin Molecule.

Glucuronic Acid

Note: Glucuronic Acid is isomeric to Galacturonic Acid.

The present view is that pectin is an acid, composed of a long chain molecule consisting largely, if not completely, of partially methylated galacturonic acid anhydride units. A high grade pectin may have a molecular weight of over 250,000. This means that well over 1000 galacturonic acid units may be strung together to form each molecule, which accounts for the viscous
nature of pectin solutions. Improper methods of preparation may result in such molecules being split into shorter fragments of corresponding lower molecular weight, lower grade,* and lower viscosity, yet of essentially identical chemical composition. (3) In other words the molecular weight is dependent upon the degree of polymerization.

Pectin may be extracted from a variety of plant materials; apples, beets, and the peel from citrus fruits are particularly rich in pectin which is obtainable by controlled dilute acid extraction.**

The extraction procedures may be varied so as to obtain pectins with more or less free acid groups, that is, the pectins may be demethoxylated to suit requirements for different purposes. The more free acid groups the more reactive the pectin is towards metal salts.

It is thought that pectin is a complex carbohydrate having the formula \( C_{70} H_{99} O_{58} \) with a molecular weight of 1866.784. The molecule is made up of eight molecules of galacturonic acid, one of arabinose, one of galactose, two acetyl groups and seven methoxyl groups.(4)

* 100 Grade means that 1 pound of pectin will "carry" 100 pounds of sugar in a jelly of standard composition and strength.

** To obtain the pectin in dry form the clarified extract may be precipitated by alcohol or it may be precipitated by certain metal salts. Both aluminum and calcium salts have been used commercially.
The physical properties mentioned may be summed up as follows:

1. It possesses absorptive capacity for bacteria and toxins. (5,6)

2. Because of its colloidal nature, it is capable of taking up large quantities of fluids; this provides bulk which helps to sweep out harmful materials in the intestines and offers a normal stimulus to peristaltic activity.

3. By its buffer action it helps to maintain a constant reaction in the intestines.

4. It acts as a protective colloid on an inflamed and perhaps ulcerated intestinal mucosa. (7)

5. Hemostatic action. (8)

6. Bactericidal action, in vitro. (9)

The interest of the general medical profession was not aroused until the apple diet was picked up from folk medicine, which brings out certain significant points as we look back on them.
HISTORY OF APPLE DIET

It is very interesting, that of all the fruits, the apple is mentioned most frequently in folk-lore. There is an old Devonshire rhyme which says:

"Ait a happle avore gwain to bed,
An' you'11 make the doctor beg his bread"

It is in the German folk customs that the original idea occurs for the use of the apple in specific ailments. In Westphalia, apples were mixed with saffron to cure jaundice. In Pomerania, to eat apples on Easter morning is believed to insure against fever. In Hesse it is said that if an apple is eaten on New Year's day, it will produce an abscess. In Silesia and Thuringia, an apple is scraped from the top to cure diarrhea, and from the bottom to cure constipation. (10)

The first mention in print of the use of fresh ground raw apple pulp in the treatment of diarrheic disorders in children and infants must be credited to Dr. August Heisler. In his book "Dennoch Landarzt", he mentions the wonderful results of apple diets as an old family remedy for acute intestinal catarrh. However, prior to Heisler's mention of this treatment, others had already advocated its uses and advantages. Hessing, a practitioner in orthopedics used apple pulp therapeutically.
peutically for vomiting and diarrhea for thirty years. It appears Heisler himself obtained his first information on the subject, from Sister Frieda Klimsch, superintendent of the Kindersanatarium in Koenigsfelt, with whom he was associated, who used this method of treatment successfully for twenty years. He used raw, unpeeled apples, and fed to adults and children, irrespective of etiology or pathology. According to him, any type of apple will do, even if extremely sour. The only essential factor is the administration of a sufficiently large quantity. The author's own child, when 15 months old, took twelve apples in one day, and was healthy after that. When the patient experiences thirst, in spite of the apples, he gives tea made with cooked apple peel. He states that not only apples have a remarkable effect, but surprising results may also be obtained with bananas. In this connection, the author mentions a letter from a sailor, who during the Chinese Expedition, was taken seriously ill with dysentery. While at Ceylon, he purchased a lot of bananas, consuming perhaps seventy to eighty. His condition thereupon became markedly improved. This occurred in 1903. (11,12)

The first clinical investigation was made and reported by Dr. E. Moro. (13) He was struck by the dramatic results recorded by Heisler, and immediately began
a controlled study of the diet. He chose mellow, ripe apples, which were peeled, cored and grated. One to three hundred grams according to the age of the patient, were given three times a day. For two days nothing else was given. It seldom was necessary to add tea at night, as the apple seemed to supply ample fluids.

After the two "apple" days, a diet without milk and vegetables was given for two days, as a transition, then the ordinary diet was given. Moro relates an interesting story of a young soldier and four or five comrades. It was in 1918, behind the eastern front, that a group were in the hospital with dysentery. Tortured by hunger, some of them ate several unripe apples, which they had spied in a nearby garden. In the hospital they received nothing but black tea. That night, their tenesmus markedly improved and their discharges of blood and mucus decreased. The following day they ate more apples, with further improvement. One of the group, who did not eat the apples, died, whereas the remainder slowly improved. Dr. Moro treated 52 cases of which 22 were acute dyspepsia, 15 dysentery, 1 typhoid fever, 8 chronic dyspepsia, 5 chronic digestive insufficiency and 1 mucus colitis. Excellent results were reported in all cases. (14)

There were other numerous European men who corroborate Heisler and Moro, and their successful use of the
raw apple diet. S. Wolff (15), 150 cases; Reye (16), 50 cases; Kaulbersz (17), 40 cases; Lennhorf (18), 185 cases; all reporting good results.

The first paper to appear in an American publication was that of Birnberg's (19) in 1933, in which he described his experiences with a large number of cases of diarrhea treated with raw apple.

Other articles appearing in American publications reporting satisfactory results with this mode of therapy, were those of Reglien (20), Kaliski (21), Giblin (22), Rowley (23), McCaslan (24), Tompkins (25,26), Borovsky (27), Manville (28), Stein (29), and Hunt (30).

A careful summary of all the case histories reported in 1937, showed that 1,021 persons have been treated for various intestinal disorders with raw apple pulp. Of these, 1,005 showed complete recovery, while 16 failed to respond. This provides a mortality rate of slightly over 1.5 per cent. This is nothing short of marvelous when it is considered that many of the patients receiving this type of therapy were not placed on this treatment, except as a last resort. (31)
RATIONALE OF THE APPLE DIET

A number of reasons have been assigned for the benefits derived from the use of the apple diet. These factors may be divided into five groups: (1) acids; (2) sugars and starch; (3) cellulose and hemicellulose; (4) vitamins and (5) pectin. Most of those who have had experience with the apple diet are inclined to believe that each factor contributes to the success of the treatment.

Borovsky attributes the beneficial action to the absorptive power of the pulp which also enmeshes mucus and bacteria, according to him. Detoxifying power is obtained through the cellulose pectins, malonic acid and tannates, which the apple contains. Maloyoth has given the most recent explanation of the beneficial action, which he fairly conclusively attributes to pectin and cellulose contained in apples. (27)

Kolbrugge (31) believes its specific action to be mainly due to increase in acids whereby the media of the bacteria are removed.

Heisler (11) believes the action of apple diets to be due to principally fruit acids, for example, malic acid, to mechanical cleansing of the intestine, and finally to the anti-inflammatory action of tannins.
present in apple. Moro (12) on the other hand, believes it to be principally a physical action due to increased bulk producing better cleansing of the large intestine, and secondarily a change of the intestinal flora.

Malyoth (32) was the first to give any concrete experimental evidence. In a detailed study he has shown that it is not the difficultly digested cellulose that the above authors believe, but it is pectins in apples which make the stool bulky. These pectins, according to Malyoth, have a strong absorbing action and considerable buffering capacity. They work then, on one hand, like charcoal, and on the other, like a protective colloid which allow the removal of astringent substances from the unhealthy lower intestine. Especially do the pectins produce a medium which efficiently absorbs bacteria, and which by virtue of this slimy property, allows bacteria to be easily removed. Malyoth does not see the beneficial effect of apples as due to one substance or one property of apples, but a combination of various mechanisms, among which are the absorbing and buffering pectins.

It has been shown that you can still get good therapeutic results after the galacturonic acid, tannic acid and vitamins are destroyed, but not if the pectin
and cellulose are destroyed.

It is known that bacterial decomposition is hindered by acid, therefore anything that would increase gastric acidity might be a factor in destroying bacteria.

Relatively small amounts of tannic acid and galacturonic acid are contained in the apple, while pectin itself, is an acid. Probably any effect from tannic or galacturonic acid would be secondary as far as killing bacteria is concerned, but bacterial decomposition is in no way a necessary condition for the occurrence of diarrhea.

It has been known for years that tannic acids are of little value in the treatment of diarrhea. The vitamins have been mentioned as having probable value in therapy, but the amounts are relatively small. The vitamins have never been shown to have any specific effect in the treatment of diarrhea.

McLester (33) states that the apple has definite laxative properties, probably due to the large cellulose content. Small amounts of vitamins A, B and C are present.

Another author (34) states pectin is the only component in the apple which, if inactive, renders the treatment ineffective. Apple treated with the enzyme
which inactivates the pectin has been found to be ineffective. Apples low in pectin are not so effective as those high in pectin. Pectin preparations, per se, have been reported to give good results equal to those obtained with the apple diet.

In reviewing other numerous articles, of which only a few above have been mentioned, it seems to be generally agreed that pectin and cellulose are the two active components of the apple. A foreign author's conclusions (35) are, that the apple diet is effective in controlling the symptom diarrhea, regardless of Etiology; it is readily administered and palatable; its effect is prompt, even life-saving, and may mean the difference between life and death.
PECTIN-AGAR

While it was found that the apple diet was effective in controlling the symptom diarrhea, there were certain inherent disadvantages in that a good grade of ripe apple was scarce in the diarrhea season; the expense was relatively high; the nursing care was excessive when several infants were being fed the apple diet; the parents and babies often objected; the diet was not well balanced; the feedings were not sterile; the apples were not of uniform therapeutic potency, and the babies almost invariably lost weight. The apple treatment retained the serious objection of all other treatments for infant diarrhea, in that we still had a starvation regime in the old apple diet therapy.

Tompkins (36) and co-workers tried a mixture of pectin for whatever its action might be and agar-agar was chosen as a source of cellulose. Agar forms a gel of any consistency desired and remains in a gel state throughout the intestine since it does not melt at body temperature. The consistency of the gel depends on the amount of agar used.

The following formula was devised as an empirical formula and controlled studies began:
The formula contained:

- Pectin - - - - - 6 grams
- Agar-agar - - - 8 grams
- Dextrin-Maltose - - 175 grams

The ingredients are mixed and kept dry. This preparation is easily kept and lasts indefinitely. The caloric content is 1020 calories, if made with milk. If the formula is made into a thick feeding which can be given to infants by bottle, the calories are 40 per ounce. If made into a gel for older children there are 51 calories per ounce.

In presenting this pectin-agar diet, Tompkins and Winters (37) presented a series of 42 infants of whom 24 were fed this mixture, and 18 were fed raw, scraped apples.

I am presenting two case histories, accompanied by photographic illustrations, to show the therapeutic results of pectin-agar in this series.

CASE I.

Child, age 6, with Flexner dysentery, having characteristic stools containing blood, pus and mucus, having had diarrhea for several days, on admission had temperature of 104° and during the first few hours was on the bed pan constantly with tenesmus and liquid stools.

He was put on standard pectin-agar formula without a preliminary starvation period. Figure 1 (next page) shows a stool within twelve hours, and Figure 2 shows
a stool 24 hours later. The patient had an uneventful recovery.

CASE II.

Child, age eight months, having Flexner dysentery with the characteristic stools containing blood, pus and

*Photograph taken from Journal of Pediatrics.
**Photograph taken from slide, owned by Dr. Tompkins, same case.
mucus, and who was almost back to birth weight, was
started on the apple diet, but continued to lose
weight, with vomiting and fever. Then protein and
lactic acid milk were tried, but no improvement noted.
The staff physician, who saw the child prior to leav­
ing for a vacation, as pictured in Figure 1, commented
after the above therapy was tried with no improvement,
that the child would be dead before he returned.

Fig. 1.

The child was kept alive by transfusions and intra­
venous glucose, and was fortified by powdered milk and
more dextro maltose, with added vitamins. So the child
was given a high caloric intake of 100 calories per
ounce - approximately two ounces every four hours. Noth­
ing else by mouth, except water. The following day,
soft stools began to appear. He had had no normal stools
for three weeks, and the vomiting stopped. On the
second day the weight curve started upward, and he
gained three or four pounds in three weeks. Figure
2 (next page) shows the result after the pectin-agar
diet.

** See footnote on previous page.
Comment: This child would have died if there had been no therapeutic agent with an adequate caloric intake. Incidentally there has been no other treatment other than that of Pectin-Agar, with adequate caloric intake, which has given therapeutic results.

Following are other interesting highlights reported in the first paper on the use of this treatment:

1. The apple fed group required an average of 6.1 days on the straight treatment, while the pectin-agar group required only 4.7 days.

2. The stools were liquid for only 1.3 days as an average in the pectin-agar group, whereas with the apple group an average of 4.1 days were required.

3. It took an average of only 3.9 days to get the

** See footnote on page 16.
infants back to a regular diet in the pectin-agar group whereas 7.1 days was the average time required in the apple group.

4. The apple group had an average weight loss of 50 grams per day. The pectin-agar group showed a gain of 75 grams per day.

5. The foregoing figures are particularly interesting in view of the fact that the pectin-agar group were more ill as evidenced by an average of 9.9 stools daily prior to treatment in the apple series as compared to 13 stools an average in the pectin-agar series. This opinion is further substantiated by the fact that only 22.7% of the apple cases had specific dysentery while the pectin-agar series included 45.8% of this type.

The following conclusions were drawn from the experimentation (37): The pectin-agar diet is a high caloric diet, not a starvation one and is helpful in treating marasmic babies with diarrhea; the preparation is palatable, having the taste of a sweetened milk formula; the formula may be adapted to give the concentrations and consistencies needed; the diet is balanced and not mainly carbohydrate as in the case of the apple diet; it is possible to return to the normal diet much quicker, since the children are already used to a milk diet of high caloric value; recurrences are
fewer; the comparative cost per calorie is low; the formula is available in all seasons; the composition is standardized, therefore always the same; the preparation of the formula is simple and may be made in the home as well as in the hospital; and lastly, pectin-agar has a psychological effect on parents. They are doubtful when the children are given raw apple, and pectin-agar seems more like a medicine.

In the latest article by Howard and Tompkins\textsuperscript{38}, a modification of the original pectin-agar mixture was made, in that they now use:

\begin{verbatim}
Pectin          - - - - - - 8.75 grams
Agar           - - - - - -  6.25 grams
Dextri-Maltose - - 125 grams
\end{verbatim}

One cup or eight ounces by volume of the resultant powder equals approximately 480 calories. This basic mixture lends itself well to the making of diets, particularly designed for nurslings and young children respectively.

In preparing a formula for nurslings one cup of the powder is cooked ten minutes in a double boiler with 24 ounces of milk. While still hot the desired amount is poured into nursing bottles. After cooking, a gel results calorically equal in milk and added carbohydrate, each ounce of which contains 40 calories. Upon rewarming
and shaking, the preparation easily feeds through a
nipple with an enlarged opening. Newborn babies take
this formula with ease and it is well tolerated and re-
tained. The usual feeding schedule is continued. Since
the calories per ounce in this mixture are twice that
usually given, the volume offered is reduced to about
one half and the difference is made up by giving water
between feedings. The end result in milk, water and
carbohydrate administration is the same as when 20 cal-
oric per ounce mixtures are given. By preparing the
pectin-agar without water it is still possible to pro-
duce the desired gel state and still maintain a well
proportioned adequate food. The low volume thick feed-
ing reduces the tendency to vomit. The prepared formula
does not give up liquids readily so hydration must be
assured by giving oral or parental fluids between feed-
ings.

For children 6 months to 2 years of age, one cup
or eight ounces by volume of the powder is cooked for
ten minutes in a double boiler with sixteen ounces of
milk or other suitable liquid. If fruit juices are used
the preparation is cooked in a part of the liquid, the
remainder being added immediately after cooking to retain
the natural flavor. Vanilla, cocoa, bitter chocolate,
fruit and other foods may be added to suit the taste. (7)
To rewarm place the container of food in hot water. The preparation may be frozen for children who prefer it cold.

The treatment of diarrheas at any age consists of limiting all intake to the pectin-agar formula and water until the stools are formed. The therapeutic result is good whether large or small amounts are taken, the bulk of the stool depending on the intake. The older infants and children are allowed as much of the food as desired. After the bowel movements are free from blood, pus and mucus, and are formed, the best practice with nurslings is to gradually replace the pectin-agar feeding with a formula in which calories from milk and added carbohydrate are equal and the volume of milk equals the volume of water, the resultant mixture being 20 calories per ounce, or with milk and carbohydrate in proportions similar to that found in the pectin-agar formula for nurslings. In a few days the infant is returned to a standard milk formula approximating a milk-carbohydrate caloric ratio of 2:1. Another method of transition is to gradually decrease the amount of pectin-agar mixture and add water when preparing the formula. After the proportions become one-half cup of the powder (240 calories), 24 ounces of milk (480 calories) and 12 ounces of water, a 20 calorie per ounce mixture re-
results with a milk-carbohydrate ratio of 2:1. At this time the special formula may be replaced with a standard milk mixture. In older children, transition is made by gradually replacing pectin-agar feedings with gelatin desserts, toast, jelly, banana, apple, baked potato, cottage cheese and lean meat. Milk, vegetable and cereal should be added with caution. An approximation of the following empirical formula was used with apple diet in the first controlled series:

1 cup to a pint, or
1 cup to \( \frac{3}{2} \) pints.

With this form of treatment they report good results in twenty three newborn infants with enteritis and they also report good results of fifty infants and children with bacillary, that were treated at home. Hospitalization is avoided because the stools promptly become formed, hydration is maintained, vomiting is minimal, calories are adequate to assure weight gain, the food is usually well taken because of the adaptability to various tastes, the infants are less fretful because of decreased tenesmus and absence of hunger and finally chronic intestinal infection is less frequent. Starvation regimes and bad tasting diets fail to fulfill most of the above criteria.

The above mentioned results have been noted, and
the authors have given some of the following results as a rationale:

**RATIONALE**

For various reasons an increasing number of clinicians deem it rational, and when possible, advisable to give high carbohydrate diets to infants suffering from acute gastrointestinal disturbances particularly if associated with parenteral infections. First, these conditions tend to decrease food tolerance by diminishing gastric secretion and by altering gastrointestinal motility with increased and sometimes reversed peristalsis. So it seems desirable to give an easily digested, simple, high carbohydrate food rather than high protein foods which because of their complex nature are more difficult to digest. Secondly, these infants have an increased metabolic rate due particularly to the hyperpyrexia. So we are dealing with increased katabolism in an individual having a digestive tract that may have a decreased ability to supply the demands. Since simple carbohydrates are easily digested and assimilated, the decreasing liver glycogen is more readily replenished and the ketosis with its possible compensatory vomiting, resulting from protein and fat katabolism, is less likely
to develop. Newborn babies, particularly prematures, often do better on a high carbohydrate formula as their caloric requirements are higher than subsequently and it is at this time that they are very susceptible to diarrhea and digestive upsets. This pectin-agar preparation fulfills the requirement of a high carbohydrate formula and in addition it is more digestible, possibly due to the acidity of the pectin, its colloidal action, and its ability to precipitate the milk into a very fine curd, a physico-chemical phenomena that doesn't alter the taste. Whatever the underlying mechanism for increasing food tolerance the fact remains that very sick infants often easily tolerate concentrated pectin-agar formulae of various carbohydrate, fat and protein combinations, even up to over one hundred calories per ounce. This preparation has been used as a basic formula to which powdered milk combinations, carbohydrates or other foods are added to increase calories in a tolerable, anti-ketogenic, low volume feeding. Such a procedure has been helpful in treating marasmic babies with or without diarrhea, prematures, or infants with vomiting, on the basis of pylorospasm or ketosis resulting from acute infections. The ease with which these pectin-agar formulae are utilized add an important factor to their rationale and usually obviate the necessity of starving
sick infants that need a normal or increased caloric intake.

In the original publications it has been shown that nickel pectinate preparations are bactericidal under proper conditions of heat and acidity. (9, 38). Arnold (41) has repeated these experiments with confirmatory findings. This work calls for additional studies as it has been proved that pectin alone has no more bactericidal properties than any other acid at a given p H. The same concentration of nickel with other vehicles of the same degree of acidity might have a similar effect on bacteria. The therapeutic effect of pectin-agar powders prepared with nickel pectinate and other pectins has been essentially the same, and the acidity of pectin is neutralized in the intestine, so it seems unlikely that the results of this treatment are dependent on a direct bactericidal effect.

Many feel, in cases of diarrhea in infants, that the bowel should be put at rest by withholding food and in some cases even water, orally. It does not necessarily follow that the empty gastrointestinal tract is at maximum rest. Some children on such a regime have almost constant green passages containing mucus and flatus. Starvation favors the ascent of B. coli into the upper bowel with secondary gas formation. This
fact plus hunger contractions superimposes the well recognized mechanism of starvation diarrhea. In such instances, upon listening to the abdomen with a stethoscope, one readily gets the impression that there is still much to be desired in the way of putting the bowel to rest. These pectin-agar diets, of the types described above, allay hyperperistalsis, and actually relatively put the bowel at rest as compared to starvation regimes, as evidenced by the prompt decrease in bowel sounds, flatus and stools even before the gel has had time to pass through the gastrointestinal tract.

Pectin and cellulose have been shown by Malyoth (5), Baumann (36), and others to be the only components in apple that, if destroyed, result in a poor therapeutic effect. Scheer (42) has reported good results from agar-milk preparations and stresses the importance of agar in mechanically giving formed stools and cleansing the gastrointestinal tract. Pectin on hydrolysis releases arabinose, galactose, methyl alcohol and up to over 90% galacturonic acid. Glycuronic acid, an isomere of galacturonic acid, has long been recognized as a chemical detoxicant for certain katabolic products and ingested poisons. Manville (36) and his co-workers report experimental evidence suggesting that pectin has the power of forming conjugation products similar to glycuronic acid.
and that the administration of pectin has a glycuronic acid sparing effect. Uronic acids are important in the syntheses of mucin and if the demands for detoxication are too great, mucus secreting elements are impaired with a tendency toward ulcer formation. Winters, Peters and Crook (43) have shown that pectin heals and prevents experimental peptic ulcers in dogs. Manville, Bradway and McMinnis (44) suggest that pectin also has a protein sparing effect by decreasing the demands for glycuronic acid formed in part from glycogenic amino acids resulting from the breakdown of body proteins.

Many articles have been published on the values of pectin as a hemostatic agent (44,45,46). Recent experimental data throws some doubt on its effectiveness in actually controlling bleeding. In the cases studied, blood did not promptly disappear from the stools, however, sooner than with other forms of treatment. The passage of blood decreased in proportion to the healing of the ulcerations, as evidenced by proctoscopic examination. It would seem, therefore, that there is more rapid healing of the bowel mucosa but no direct hemostatic effect.

The role of pectin per se in controlling the symptom diarrhea seems to be as yet not completely determined. Block and his co-workers (47) report that nickel pectinate
is effective in treating acute and chronic dysentery. Due to the natural tendency for remissions and exacerbations of symptoms in these cases, regardless of therapy, it is difficult to draw conclusions from a small series. These authors state that pure pectin is ineffective. This opinion is not held by others who report good results in treating various types of diarrhea with pure pectin (48, 49, 50, 51), however, Wilke lays more stress on the systemic improvement and states that pectin does not produce as well formed stools as apple or banana. Experience with the University of Indiana group in treating both adults and infants with nickel pectinate revealed no definite help in controlling the liquid stools; in fact, in most instances evacuations became more liquid and frequent; so that it was necessary to discontinue the therapy. There was, however, possibly some evidence of systemic improvement. In their experience the use of nickel pectinate alone has been unsatisfactory in treating infants and children. Any improvement systemically has been offset by a lack of control of the diarrhea or an exacerbation of the symptom. Their results have been equally good whether nickel pectinate or other pectins have been used in the pectin-agar powder. Any treatment to be satisfactory during infancy must control the liquid stools promptly. So the sum total effect of the
pectin-agar-dextrin-maltose formula may be summarized as follows: 1) Pectin retains any value it may have as a detoxicant, adsorbent, absorbent and healing agent and, 2) is in a vehicle which promptly controls the symptom diarrhea. 3) The preparation results in a high calorie, high carbohydrate, well tolerated food which tends to combat ketosis and vomiting.

**SUMMARY**

1. Details of preparing and administering pectin-agar formulae for nurslings and older children are simply cooking 8 ounces by volume of pectin-agar powder into 24 or 16 ounces of milk.

2. A series of 23 cases of enteritis in the newborn are reported with complete recovery of all. Nine infants in the group were treated with pectin-agar formulae which proved helpful and practical.

3. The excellent results in treating older infants and children are discussed. The simplicity and effectiveness of the pectin-agar regime is shown to lend itself particularly well for treating infants and children at home.

4. The rationale of this therapy depends on the combined effects of the pectin-agar combination in well tolerated, anti-ketogenic, highly nutritious formulae.
HEMOSTASIS

The foreign literature reveals that pectin has been used for the purpose of arresting hemorrhage for some time. For years it was the custom in Austria to apply sliced apples to bleeding wounds. However the first scientific paper on the use of pectin as a hemostatic agent was by Violle and St. Rat in 1924 (52). On experimenting they found that 50 to 80 cc of pectin per os is non-toxic and is not followed by any bad effects and these doses could be repeated the following day. They also found that man shows no anaphylactic reactions or shock if the pectin is given by mouth. They state that patients do not exhibit any change in blood except an increased coagulability from one fourth to one third in time. They mention that the pectin increase in coagulation reaches its maximum effect in two hours or more after ingestion and continues eight to twelve hours. Another finding was that hemorrhages are definitely arrested after 40 to 60 cc has been ingested.

In a later paper, Violle (53) says to get the maximate effect from the pectin you must give juices high in pectin.

In 1935 Kochs (54), reports one case of ulcerative colitis and another which had severe rectal hemorrhages in which pectin (Sangastop) was used both by mouth and
by enema with improvement. He also used pectin tampons in three cases of hematemesis with good results.

Other experiments were tried by Brahn, Klarenbeck and Kangner (55) in which they used various means of administration -

(a) Per os they report coagulation reduced from normal of three minutes to a minimum of 3 seconds after four and one half hours.

(b) Intra-muscular and subcutaneous injections showed the action began after three hours with reduction from two and one half minutes to fifteen seconds in coagulating time.

(c) Intravenously - even in small doses, action was found to be immediate and lasted hours. They believe the acid properties of a colloid is important as a means of action.

Another author used pectin injected subcutaneously in jaundice cases and in cases of uterine hemorrhage with good results. (6)

Gohrbandt (3), in 1935, at the Surgery Congress, reported on 100 patients who had been treated with Sangastop. They were given 20 cc. of Sangastop on two consecutive days and a 20% increase in the coagulation time was noted. His method was to give 20 cc of a 115% solution intra-muscularly and his coagulation studies
were made by the Burker apparatus. He noted as soon as 10 minutes resulted in acceleration of blood coagulation which on the average attained its maximum in about 40 minutes. Another remarkable thing was noted in that the effect lasted for as long as six days.

He followed these studies by the pectin given by os - a 5% solution used, giving one tablespoonful on three consecutive days; following this he noted the beginning of acceleration did not set in until after forty-five minutes, but the duration was not as long when taken per os. Intravenous administration showed the acceleration or prolongation did not exist as compared to intramuscular injection. He reports good results in hepatic lesions, in cases that succumb to after bleeding in surgery and cases of obstructive jaundice pre and post-operatively. He recommends Sangostop to be used in all pathological conditions prophylactically and therapeutically which are attended by pathologically prolonged coagulation time.

Sack (56) reports good results with Sangostop used intra-muscularly and intravenously in 32 cases of which 10 were gastro-hemorrhages, 7 pulmonary hemorrhages, 3 kidney and bladder hemorrhages, 2 bowel hemorrhages and six otherwise; 3 hemophilias and one icterus.

Feriz (57) reports good results in breast operative
in which Sangostop was given intramuscularly, in which the bleeding was noticeably less. Other operative cases were prostectomies, herniorrhaphys and thyroidectomys with good results in decreasing bleeding.

Langer (58) states that of ninety-six cases, mostly tonsilectomy, treated with Sangostop, there were ninety-five that demonstrated clearly the hemostatic properties of this remedy. One case showed no effect. Sangostop is therefore a welcome means of alleviating all parenchymatous bleeding by tampons, although the effect is not easily expressed in exact quantitative terms. It is absolutely harmless, never causes anaphylactic reactions, but does measurably speed up the coagulation of the blood. The preparation is therefore a meritorious acquisition. He used it for exterior application in the form of compresses, soaked in a 5% solution.

Tompkins and co-workers (59) carried this work out experimentally with reliable technique, using Sangostop intra-muscularly and orally, on eight dogs and five hemophiliacs with unfavorable results in all.

In the experiments by the foreign authors, clinically there were no contra-indications or implications, in the use of pectin for hemostatic purposes. Nearly all the comments by the foreign authors were to the effect that pectin was harmless and that large doses were
well tolerated. Their results show that pectin solutions will give untoward effects. In preliminary dog experiments and on several occasions they noted that too rapid administration of the pectin solution produces nausea, vomiting, defecation, urination and general prostration, lasting for a period of ten to twenty minutes or more.

In addition, they studied histological sections taken after three days from the muscular area injected, and these sections showed a local inflammatory reaction.

In conclusion, it would appear that in view of this, we should not take some of the current theories too literally. They are obviously trying to commercialize it. It is still questioned, and has not been proven.
Tompkins and Haynes (9) demonstrated that pectin had bactericidal action under certain conditions. Later, in subsequent work (40) it was shown that the bactericidal action which had been observed was due to nickel in the pectin first used, and not to pectin per se. Clinical evidence has accumulated to show that other pectins as well as the nickel pectin mixture have definite value in the treatment of wounds (60).

Pectin powder was used in aqueous solutions in percentages which vary according to the case to be treated. Solutions ranging from 2% (on the basis of 100 grade pectin) to as high as a thick paste of 10% have been used. The desired amount of pectin is weighed and mixed rapidly in cold water. For many of the cases the solution was sterilized in the autoclave for twenty minutes at 15# pressure, but the addition of merthiolate makes sterilization by heat unnecessary and permits the use of a lower percent of pectin, as heat reduces the viscosity. It was found that solutions of pectin may become contaminated with fungi, which can grow in it, being favored by the acidity of the solution (pH 3.4 - 3.8). To prevent this aqueous merthiolate was added to make a dilution of 1-200,000. This not only prevented growth
of fungi but added to the bacteriocidal effect of the solutions and yet was dilute enough that it was not toxic to tissue (61). Sterile gauze dressings are saturated with the pectin solution or the solution is applied directly to the lesions as needed. The dressings are changed as often as necessary to keep them moist. Since this is an aqueous carbohydrate solution, excessive evaporation results in a tenacious stiff dressing which is difficult to change without tearing away new tissue. However, the pectin solutions give up the moisture slowly and by using vaseline gauze, oiled silk, heavy waxed paper or Parafilm over the pectin dressings with a dry dressing over that, evaporation was reduced to a minimum. When used following sequestrectomies the pectin dressings were changed two or three times a week; dressings of other types of wounds, usually at least once a day.

This therapy has been used over a period of three years on 75 cases with lesions of various kinds. The cases treated were of the following types: chronic discharging wounds such as osteomyelitis, superficial wound infections, operative wounds with secondary infection, operative wounds with drainage, traumatic wounds and ulcers, trophic and decubitus ulcers. Before the pectin
treatment was started the condition of the wound was described as fully as possible, a bacterial culture was taken, and a clinical photograph was made. Progress of the wound was followed by bedside notes, occasional bacteriological examinations and clinical photographs.

The following case history, with accompanying photographs, demonstrates the result of one of these cases:

CASE I.

J. C., white male, age 4 years, admitted 9-23-36. Physical examination and history essentially negative except for contused and lacerated tear on the left foot which had resulted from a street accident on 9-22-36. Lesion had been closed with a primary suture at the time of the accident. At the time of admission (Figure 1)

some necrosis was believed present but it was thought

** See footnote on page 16.
best not to do a debridement. Antitetanus serum was given and continuous bath of one-fourth chlorozone administered. The child's temperature was irregular up to 104°F. The local discharge persisted and the general condition became alarming to the extent that amputation was considered. The stitches were removed to assure adequate drainage, and the metatarsals and some of their joints were found to be exposed.

On 10-8-36, dressings of 2% nickel pectin solution without merthiolate were started. The discharge from the wound decreased, and healthy granulation tissue proliferated at a very satisfactory rate. The temperature and general condition was improved promptly and on 10-22-36, the condition was satisfactory enough to transfer the child to the convalescent hospital where treatment was continued. On 12-12-36, at time of discharge, the wound was healed except for a small area of granulation tissue on the dorsum of the foot (Figure 2).

![Figure 2](image)

**Fig. 2**

The child had perfect motion of the foot, although an ankylosis of the involved joints had been expected.

** See footnote on page 16.**
Pectin dressings in the types of wounds treated bring about a prompt visible change in the wound. There is a rapid disappearance of the purulent foul drainage, and, in many cases, a reduction of the objectionable odors. The wound takes on a healthy appearance and fills in from the bottom with rapid formation of granulation tissue. This granulation is of a distinctive smooth, bright red type with a healthy glistening sheen, seems firm, and shows vigorous growth.

No essential difference has been observed in the results of the treatment of wounds with pectin free of nickel and merthiolate and those treated with the nickel preparation with and without merthiolate. The bactericidal effect of aqueous solutions of pectin, because of the high hydrogen-ion concentration (62), and of the nickel and merthiolate, when present, appears to be only a part of the total therapeutic action. A considerable portion of the curative effect might well be due to the hygroscopic property of pectin solutions which results in the decrease of edema in the granulations and leads to healthy wound healing. The granulation tissue thus formed, which is actively growing and apparently not edematous, seems to be able to rid itself of the effects of the infecting bacteria. The mechanical removal of organisms, pus and serum with change of dressings is
also probably of some benefit.

The acidity of the material does not seem to cause any irritation to tissue. Early in the course of treatment the blood and pus in the wound decrease the acidity of the solution considerably, but at later stages of healing when very little body fluid is present, there is also no evidence of irritation. On the contrary, the application of pectin dressings to various types of lesions seems to decrease the discomfort of the patient, particularly in infected operative wounds.

They do not feel that the pectin has any direct stimulating influence on epithelization; in fact, there are some indications that pectin inhibits that stage of healing. Accordingly, when a wound is clean and has filled to the desired degree, other medications are used to keep the lesion clean while the epithelial tissue grows. Much has appeared in foreign literature concerning the hemostatic action of pectin. However, they have been unable to observe positive clinical evidence to substantiate these claims for such marked local hemostatic action. Experimental work with animals in which they used various pectin solutions to test for general and local hemostatic action, following intra-muscular and intravenous injections and local application gave
evidence of some hemostatic action, but of such a slight and transitory nature that its significance seems questionable.

Thomson (63) reports the use of 2% pectin solutions in the treatment of old infected burns, pressure sores, infected soft tissue wounds, osteomyelitis, and infected compound fractures. He felt that it materially diminished the healing time of infected wounds as compared with other known methods.

They realize that it is very difficult to determine the relative efficacy of various therapies, since case differences make controls impossible except in the broadest sense, and often results depend not only on the local measures used, but on the entire treatment. However, with most of their patients, the results exceeded the usual expectations. In many instances, wounds that had been treated by the customary measures with no success, showed prompt response to the pectin therapy. The method seems to be of particular value in the old chronic type of lesion which often resists all therapeutic efforts.

They concluded that after more than three years of pectin solutions in the treatment of a sizable ser-
ies of various types of wounds, they feel that such therapy results in a very prompt response, with cleaner wounds, and a rapid growth of highly vascular granulation tissue.
CONCLUSION

In this review of the literature, it has been proven beyond a doubt, that pectin has a remarkable therapeutic value in the treatment of diarrhea in infants and children.

Although it is still in the experimental stage in the treatment of hemorrhages and wounds, continued research may prove it of definite value.

It is very gratifying to know we have a new therapeutic agent of such definite value. Incidentally, at a meeting of a group of Pharmacists at the Indiana University it was decided that pectin is one of the three drugs of most current interest. Undoubtedly, the progress of research on this subject will be very rapid, and within a few years, this paper will be only a brief, in the review of its therapeutic uses.
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