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## PRESENT VIEWS IN RESPECT TO MODES AND PERIODS OF INFEC- TION IN TUBERCULOSIS \*

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In considering the various modes in which infection with the tubercle bacillus can occur, we may, for the purposes of this paper, leave out of discussion all except inhalation and ingestion. There is practically no difference of opinion concerning their relative importance. They play small part in the epidemiology of the disease, and the total number of cases due to them is insignificant compared to those in which infection takes place through the respiratory and the digestive tracts. Both routes of infection are universally recognized, and there remains to be determined now only their relative importance as portals of entry.

Tuberculosis is a disease, the lesions of which are found so preeminently in the lung that it is easy to understand how the older physicians considered the respiratory tract the route of invasion. The classic work of Arnold gave scientific standing to this idea, since it proved that the lung could be invaded even by particles of inert matter, such as lampblack, introduced by the respiratory tract, and the experiment of Cornet, who exposed guinea-pigs to the dust produced by breaking up dried tuberculous sputum with a broom, resulting in the infection of most of the animals, seemed to settle the question in favor of this method from a practical point of view.

The older observations were apparently lost sight of, and did not receive due consideration until after the memorable British Congress on Tuberculosis in 1901, when the attitude of Koch in regard to the danger of bovine tuberculosis and the alleged rarity of primary intestinal tuberculosis brought them to the front once more.

### RESPIRATORY INFECTION

The work of Arnold and the experiments of Cornet have been mentioned as furnishing the basis for the belief that tuberculous infection took place mainly through the respiratory tract. Further evidence seemed to be at hand in the greater number of cases in which the supposedly primary lesion was found in the lung and bronchial lymph nodes as compared with the intestine and mesenteric glands. The value of this evidence has been weakened during recent years

by the discovery of the fact that, in children particularly, the bronchial lymph nodes are often tuberculous when no change can be found in the lung; and the belief is growing that the bronchial glands and small lymph nodes are first infected, and the lung tissue becomes involved later. Schroeder and Cotton have demonstrated that infection of the lung and bronchial glands can result from inoculation into the most distant parts of the body. A calf inoculated under the skin at the end of the tail died affected with tuberculosis of the lungs. The bronchial mediastinal and mesenteric glands were edematous and contained tubercle bacilli, though not having the histologic changes of tuberculosis.

Three hogs inoculated in the same way developed progressive tuberculosis of the lungs, liver and inguinal glands, and in one the gastrohepatic and bronchial glands were involved.

It is evident that infection of the lung is not the simple process of inhaling bacilli directly into the alveoli, as was formerly believed, but involves a more complicated mechanism.

The fixing of the portal of entry by the so-called oldest lesion is also open to serious question. I have produced fatal pulmonary tuberculosis in monkeys by feeding, with very insignificant intestinal lesions. All the oldest lesions were located in the lungs and bronchial glands, yet the method of feeding largely precluded the possibility of the tubercle bacilli reaching the lung except through the digestive tract. Practically all observers agree that in children there is a marked tendency to rapid and general dissemination of the disease, and many note that it is frequently impossible to determine the oldest lesion. As our conclusions have been drawn largely from postmortem observations on children, these facts are significant.

*Dust and Spray.*—In regard to the form in which tubercle bacilli are inhaled, all are agreed that dust from dried and pulverized sputum, and mouth spray produced in coughing, talking, sneezing, etc., both play their part. The relative danger of the two methods has not been determined, some believing that dust is the chief menace, while others follow Flüge in holding that the mouth spray produces infection more readily. The bacilli in the spray are certainly more apt to be alive and virulent. Both must be recognized as capable of producing infection, and droplet infection is probably the more dangerous.

### INFECTION THROUGH THE DIGESTIVE TRACT

The first recorded cases of infection through the digestive tract are those of Klenke, who in 1846 gave the histories of sixteen children who had been fed on cow's milk, and all of whom showed tuberculosis of the intestines, glands, skin or bones.

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Previous to this, however, Carmichael, in 1810, recorded as his observation that he had frequently seen the mesenteric glands strumous without involvement of the external glands, and this led him to believe that in scrofula the mesenteric glands were first involved. He referred to the frequency of a disease similar to scrofula seen in pigs fed on sour milk, and called attention to the common occurrence of bowel trouble in children at the time of weaning "too often followed by disease of mesenteric and lymphatic glands."

Casper, in 1882, referred to the extent of tuberculosis ("nodular consumption") among the milch cows of Paris, and said, "It is possible that there is a connection between this phenomenon and the many tuberculous diseases among the children of Paris."

Experimental evidence of tuberculous infection in cattle by feeding was given as early as 1868, by Chauveau, who extended his work with corroborative results in 1872 and 1873; and Villemain in 1869 obtained positive results by feeding in rabbits and guinea-pigs. He was the first to employ a tube for the introduction of tuberculous material into the stomach. Experiments by scientists of every nation have given positive support to the work of these early observers. It is also a well-known and widely observed fact that in the spread of tuberculosis of cattle and swine the digestive tract plays a most important rôle. Swine particularly are infected through the digestive tract in the great majority of cases, and the ingestion of milk from tuberculous cattle is universally recognized as one of the chief factors in the spread of the disease among these animals. The first examination made by the officers of the federal Meat Inspection Service is based on this fact. In 93.3 per cent. of cases, tuberculous hogs show infection of the cervical glands.

"As the disease is essentially produced by ingestion, the glands and tissues associated with the digestive tract are the most frequent seats of infection. Indeed, the superior cervical glands (in almost all cases the submaxillary gland) are nearly always affected, as at the postmortem examination held by bureau inspectors over a consecutive period on 120,000 tuberculous hog carcasses, 93.3 per cent. were found to contain lesions in these glands. The large tonsils and the large number of lymph sinuses in the lymph glands probably account for this great frequency."

"From some records relative to the locations of tuberculous lesions in cattle that were made at the same time that the figures pertaining to hogs were collected, it appears that in tuberculous cattle the lesions of tuberculosis were located in the cervical glands in 66½ per cent. of the animals, in the bronchial glands in 54.5 per cent., and in the mediastinal glands in 63.6 per cent."

In 1901, in his London address, while discussing the relation of bovine tuberculosis to human health, Koch took the ground that infection through food could be assumed to have taken place with certainty only when the primary tuberculous lesion was located in the intestines. He asserted that this was rarely found to be the case, and argued that the danger of infection through food was slight. The stand taken by Koch assumed that the tubercle bacillus was unable to gain entrance to the system through the intestinal wall without the production of a lesion at the point of entrance.

The question raised by Koch has been thoroughly investigated, and it can be said with certainty that the tubercle bacillus can penetrate the mucous membrane of the upper digestive tract as well as that of the intestine readily and quickly, without producing a tuberculous lesion at the point of entry. By Baumgarten,

however, it is held that there is always a focus of infection at the point of entrance sooner or later, even though it may be microscopic. Against this is the demonstration by von Behring and Roemer of the ready permeability of the intestinal mucosa of young animals by various bacteria—even the large anthrax bacillus. In 1,000 swine, infected through food, Oster-tag found the glands of the throat, neck and mesentery tuberculous, while the mucous membrane of the intestine was always free from disease. Orth, in 1879, and Cornet, in 1880, observed bacilli pass step by step through the fully developed mucous membrane of the uninjured intestine and reach the lymph channels and mesenteric glands, leaving no recognizable trace behind (Furst). Dobroklonski, in 1890, working under Cornil, showed that the tubercle bacillus would quickly penetrate the healthy wall of the intestine in guinea-pigs. Desoubry and Porcher, students of Nocard, showed in dogs that during the digestion of fats large numbers of bacteria were carried through the intestinal wall and could be detected in the chyle within a few hours after the meal was given. If food free from fat was given, few or even no bacteria could be found. Nicolas and Descos, in 1902, found that tubercle bacilli given to dogs in fatty food reached the chyle within three hours. During feeding experiments conducted at the laboratory of the State Live Stock Sanitary Board of Pennsylvania, we frequently observed extensive tuberculosis of the lungs and thoracic glands in animals which showed slight or even no involvement of the intestine. In 1902-1903, I introduced into the stomachs of a number of dogs tubercle bacilli suspended in an emulsion of melted butter and warm water, using a tube in order to prevent possible infection through the trachea. The dogs were killed after three and one-half to four hours, during active digestion, as much chyle as possible was collected, and the mesenteric glands were removed. Guinea-pigs were inoculated with this material. Tubercle bacilli were demonstrated in abundance in eight of ten experiments. The dogs were kept on soft food for some days before the experiments, and were purged with castor oil, in order to rid the intestine of all foreign matter which might injure the mucous membrane. Numerous sections of the intestine were examined also, but no injury could be detected.

It is possible here only to mention the work of Calmette and his students, as a result of which he concluded that pulmonary tuberculosis acquired at any age may be due to recent intestinal infection.

The rapidity with which tubercle bacilli penetrate the intestine and reach the lung through the thoracic duct is remarkable. Besanti and Panisset found that when fed to dogs in soup they reached the heart blood within from four to five hours. Bartel found that after a single dose they penetrated the uninjured intestine and reached the mesenteric glands during the following digestive period. Schlossmann and Engel, by inoculating tubercle bacilli suspended in cream into the stomachs of young guinea-pigs through an incision in the abdominal wall, demonstrated that they reached the lung within six hours. Their work has been confirmed by Ravenel and Reichel. Rabinowitsch and Oberwarth established nutrition through a gastric fistula in swine, and then resected the esophagus, after which tubercle bacilli were introduced into the stomach. Within twenty-four hours they were shown to have penetrated to many organs of the body.

## INFECTION BY THE BOVINE TUBERCLE BACILLUS

The statement of Koch in 1901 that bovine tuberculosis was not a menace to public health has also led to a vast amount of study which throws light on the portal of entry of the tubercle bacillus. It is conceded by every one that bovine tuberculosis is found almost exclusively in children under the age of 16 years, and that the susceptibility to this type of infection is greater during the first five years of life than it is afterward. It is perfectly evident that the only exposure that children of this age can have to the bovine germ is through the food which they eat, and infection is, therefore, invariably through the digestive tract.

The results of the English royal commission, the German imperial commission, and numerous private workers have been frequently quoted, and I give in Table 1 a summary of instances collected by Dr. Park which indicates fairly the amount of infection due to the bovine tubercle bacillus, especially in fatal cases.

Many nonfatal cases of tuberculosis are also caused by the bovine germ. These are found almost exclusively in children, and the infection is through the digestive tract.

Fraser, in sixty-seven cases of bone and joint tuberculosis in children under 12 years of age, found the bovine germ forty-one times, the human twenty-six times, and both three times.

TABLE 1.—INFECTION DUE TO THE BOVINE TUBERCLE BACILLUS IN INSTANCES COLLECTED BY PARK

Persons	Age	Total Number	Cases	
			Human	Bovine
Adults, 16 years and over.....		955	940	15
Children, from 5 to 16 years.....		177	131	46
Children, from 0 to 5 years.....		368	292	76

Mitchell examined seventy-two children under 12 years of age with cervical adenitis, and found the bovine germ in sixty-five, the human in only seven.

It should be remembered that the human tubercle bacillus is capable also of producing infection through the digestive tract, and the mistake must not be made of considering only those cases in which the bovine germ is found as due to ingestion.

## INFECTION THROUGH THE TONSILS

The frequency of infection through the tonsils has been recently called in question by von Pirquet, who quotes Albrechts and Ghon to support his view. The former in 1,060 cases found only three instances of primary tonsillar infection, and the latter in 189 cases found only one. It is hard to reconcile these findings with those of others, or with experimental work.

Wood has collected from the literature 1,671 instances, eighty-eight (5.2 per cent.) of which showed primary tuberculosis. These examinations were made by various methods, and probably fall short of the truth. Lartigau and Goodale have shown that systematic inoculation of animals gives a higher percentage of tuberculosis. In seventy-five cases, Lartigau found twelve (or 16 per cent.) tuberculous. Dieulafoy, by the inoculation of guinea-pigs, found tuberculosis of the tonsils in fifteen of ninety-six cases. This work has been criticized on the ground that no histologic examinations were made, as Dieulafoy was not careful to exclude the crypts, which may lodge tubercle bacilli. Latham, however, who avoided these sources of error, in twenty-five consecutive necropsies on children from 3 months to 13 years of age, found seven which

were tuberculous—results practically identical with those of Dieulafoy. Confirmatory reports have been made by a large number of observers, many of which are included in the figures quoted from Wood. The susceptibility of the tonsils to tuberculous infection is shown by the examination of persons dead of phthisis.

Experimentally, the tonsils are readily infected, by direct application, as well as by feeding tuberculous material. In a series of experiments which I carried out at the laboratory of the State Live Stock Sanitary Board of Pennsylvania, swine fed with tubercle bacilli from man and from cattle developed generalized tuberculosis, with marked involvement of the tonsils, apparently primary, with necrosis and ulceration.

The experiments on these lines are too numerous to review here. Practically all experimental observers have noted the susceptibility of the tonsils to tuberculous infection. Wood of Philadelphia has carried out a most instructive series of experiments on swine. He found that the application of tubercle bacilli to the back of the mouth rapidly produced primary tuberculosis of the tonsils, soon followed by involvement of the submaxillary and cervical glands and extensive disease of the lungs. The mesenteric and bronchial glands were always diseased in about an equal degree.

I have referred above to experiments carried out on monkeys by feeding, in which the lungs showed extensive and destructive tuberculosis. In these animals, while no lesion of the tonsil could be found, caseous lymphatic glands were found in the neck in the region draining from the throat, and there could be no doubt that a part of the infection at least occurred by penetration of the mucous membrane in this region.

Grober believes that infection through the tonsil is the most frequent origin of apical tuberculosis. His experiments have demonstrated that from the cervical glands there is a direct route to the pleurae and lungs, and that this leads especially to that portion of the lung most frequently the primary seat of tuberculosis—the apex.

The evidence that the tonsils are frequently the portal of entry for the tubercle bacillus appears to me very conclusive, and it seems equally certain that food is the bearer of the infection in a large proportion of cases.

## PERIOD OF INFECTION IN TUBERCULOSIS

Few problems offer more inherent difficulties in their solution than the determination of the age at which tuberculous infection occurs. It is easy to construct tables showing the age at which the disease becomes manifest clinically, but, except in the early years of life, these give little clue to the exact time of infection.

There is no doubt of the existence of a widespread opinion that infection takes place chiefly in infancy and childhood, and this opinion appears to be growing. It seems to have a legitimate basis, even if not wholly true. In 1900, Naegeli showed by necropsies in Zurich that by the age of 30, 99 per cent. of persons showed tuberculous lesions or scars, results which have been in a measure confirmed in other cities, but which cannot be accepted as correct for the general population.

The use of tuberculin by the method of von Pirquet, or some of its modifications, is even more directly responsible for the belief in early infection. Von Pirquet himself obtained positive reactions among

children of the poorer class in Vienna in a surprising number of cases—70 per cent., if clinical cases of tuberculosis are excluded, and 80 per cent. if included, as shown by Table 2.

More surprising even are the results of Hamburger and Monti, also on children of the poorer class in Vienna (Table 3).

Based on such findings, the belief is widely held that over 90 per cent. of children are infected with tuberculosis by the 14th year, and statements have been made that tuberculosis in adult life is only the recrudescence of infection acquired in early life.

A further study of reports from different parts of the world reveals marked variations in the percentage of positive reactions, but all show that tuberculous infection in childhood is extremely common, as seen by Table 4.

Postmortem reports by von Pirquet, Müller and others show that the positive reactions fall short of showing the full number of those infected.

Turning to recent work in the United States, we find a somewhat different picture. Veeder and Johnston tested 1,321 hospital children in St. Louis, and obtained a maximum of 48 per cent. positive reactions at the age period from 10 to 14, including cases of clinical tuberculosis, and 38 per cent. exclusive of these.

Cattermole of Colorado, in a series of sixty-six cases from 1 to 14 years of age, found twenty-five, or

TABLE 2.—POSITIVE REACTIONS IN CHILDREN OBTAINED BY VON PIRQUET

Age (Yrs.)	Including (Cases of Tuberculosis)			Excluding (Cases of Tuberculosis)		
	Total No.	Positive Reactions— Number	Per Cent.	Total No.	Positive Reactions— Number	Per Cent.
Under 1.....	410	21	5	388	0	0
From 1 to 2.....	116	24	20	89	0	0
From 2 to 4.....	208	74	35	162	22	13
From 4 to 7.....	264	127	48	189	53	30
From 7 to 10.....	216	138	64	154	74	48
From 10 to 14.....	193	155	80	147	105	70

TABLE 3.—POSITIVE REACTIONS IN CHILDREN OBTAINED BY HAMBURGER AND MONTI

Age (Years)	No. Children Tested	Positive Reactions—	
		Number	Per Cent.
Under 1.....	23	0	0
From 1 to 2.....	46	4	9
From 2 to 3.....	56	11	20
From 3 to 4.....	75	24	32
From 4 to 5.....	50	26	52
From 5 to 6.....	63	32	51
From 6 to 7.....	46	28	61
From 7 to 8.....	30	22	73
From 8 to 9.....	35	25	71
From 9 to 10.....	26	22	85
From 10 to 11.....	29	27	93
From 11 to 12.....	19	18	95
From 12 to 13.....	17	16	94
From 13 to 14.....	17	16	94

TABLE 4.—PERCENTAGE OF POSITIVE REACTIONS IN CHILDHOOD OBTAINED BY VARIOUS OBSERVERS

Name	Place	Number Tested	Age	Positive Per Cent.
Øverland,	Bergen,	843	From 12 to 14	50
Amenta,	Palermo	800	From 8 to 12	83
Müller,	Vienna	949	From 10 to 14	54
Calmette,	Gryez	1,226	From 5 to 15	81.4
Letulle,	Lille	...	From 12 to 16	60

38 per cent., of positive reactions. Taking the age period from 10 to 14, his positive reactions reached 63 per cent.

Cattermole quotes Manning of Seattle as having obtained 58.1 per cent. of positive reactions at the age period from 10 to 15, in a series of 228 children.

He also quotes Fishberg of New York, who, among 692 children living with tuberculous parents in the

tenements, obtained 67.25 of positive reactions, while among 588 of the same class, but living with nontuberculous parents, 52.72 per cent. gave positive reactions.

Smith subjected 1,225 Indian children in New Mexico of school age to the test, and obtained 760 positive reactions, a percentage of 64.40.

TABLE 5.—TOTAL REACTIONS, INCLUDING CASES OF CLINICAL TUBERCULOSIS

Age (Years)	No. Children Tested	Positive Reactions—	
		Number	Per Cent.
Under 1.....	224	25	11
From 1 to 2.....	137	34	24
From 2 to 4.....	188	57	30
From 4 to 6.....	206	68	33
From 6 to 8.....	182	74	40
From 8 to 10.....	157	69	44
From 10 to 12.....	115	45	40
From 12 to 14.....	112	54	48
	1,321	426	

TABLE 6.—REACTIONS IN CHILDREN WITHOUT CLINICAL MANIFESTATIONS OF TUBERCULOSIS

Age (Years)	No. Children Tested	Positive Reactions—	
		Number	Per Cent.
Under 1.....	202	3	1.5
From 1 to 2.....	109	6	5.5
From 2 to 4.....	163	32	19
From 4 to 6.....	172	40	23
From 6 to 8.....	152	44	29
From 8 to 10.....	126	38	30
From 10 to 12.....	107	37	34
From 12 to 14.....	94	36	38
	1,125	236	

These findings are corroborated by postmortem examinations done on children who have died from various diseases.

The studies of Harbitz throw much light on this question. I give his results, as well as those of others, most of which are quoted from his monograph:

Harbitz, in 275 necropsies on children under 15 years of age, found 117 (42.5 per cent.) of tuberculosis.

Babes, in 902 necropsies on children under 15, found tuberculosis in 288 (31.9 per cent.).

In 1887, in ninety-three necropsies, tuberculosis of the bronchial and mesenteric glands was found sixty-five times. In only thirteen was death caused by tuberculosis.

Geill, in 902 necropsies on children under 15, found tuberculosis in 288 (31.9 per cent.). The maximum was reached at the period from 6 to 9, 46.9 per cent.

Müller, in 500 necropsies on children, found 150 (30 per cent.) cases in which death was due to tuberculosis, and fifty-nine (11.8 per cent.) of latent tuberculosis.

Hecker, in 700 necropsies on children, found active or latent tuberculosis in 147 (21 per cent.).

Monrad, in 654 necropsies on children, found tuberculosis in 157 (24 per cent.).

At the pathologic institute of Kiel, in 2,572 necropsies on children under 15, tuberculosis was found in 16.7 per cent.

Boltz, in 2,601 necropsies on children under 15, found tuberculosis in 428 (16.1 per cent.). Exclusive of those under 1 year of age, we have 1,171 necropsies with tuberculosis in 364 (31 per cent.).

Heller found latent tuberculosis in 140 (19.6 per cent.) among 714 children dead of diphtheria.

Councilman, Mallory and Pearce, in 220 necropsies on children dead of diphtheria, found latent tuberculosis in thirty-five (16 per cent.).

Hand, in 332 necropsies on children, found tuberculosis in 115 (34.6 per cent.).

Still, in 769 necropsies on children under 12, found tuberculosis in 269 (35 per cent.). In forty-three it was latent, and in 117 (43.4 per cent.) before the second year.

Many other similar reports could be given, but these have been selected as covering a large part of the world, and representing fairly the occurrence of tuberculosis as found postmortem in children.

Wallgren of Upsala has made some valuable clinical observations bearing on this subject. He compared the histories of 100 consumptives and 100 healthy persons as to their exposure during childhood. He took only those cases in which intimate contact during childhood with coughing consumptives could be affirmed with reasonable certainty. "Of the 100 tuberculous patients, fifty-one gave evidence of childhood contact with tuberculous associates, whereas of the 100 normal individuals, such contact was found in but thirteen."

It is impossible to escape the conviction that childhood is preeminently the time of life when the tubercle bacillus gains a foothold in the body.

#### ADULT INFECTION

The difficulty, especially marked in adult life, of connecting the clinical manifestations of tuberculosis with the date of infection, has already been mentioned, but fairly accurate information on adult infection can be obtained by the careful study of groups of individuals of good family history especially exposed to infection for considerable periods, such as physicians and attendants at hospitals and sanatoriums for tuberculosis, and those who marry consumptives. A number of collective investigations are quoted by Cornet and other writers. Many of these, owing to incomplete data and other defects, are of little or no value. From the material at hand I have tried to select those which seem to throw some light on the question.

Saugman states that of 174 sanatorium physicians, whose average term of service was three years, and whose subsequent history was followed for three and one-half years, only two became tuberculous. Among sixty-four laryngologists from eight different clinics, none contracted tuberculosis.

Williams has, in two papers, given most interesting facts concerning infection of physicians and attendants at Brompton Hospital, founded before the discovery of the tubercle bacillus, and before the contagiousness of tuberculosis was recognized. His first paper gave the statistics of the hospital staff from its foundation in 1846 to 1882, thirty-six years. Among four resident medical officers, one of whom held office twenty-five years, no case of consumption has developed. Among 150 house physicians, none of whom held office for less than six months, and many much longer, only eight cases of consumption occurred.

The second paper gives the results from 1882 to 1909. It includes resident and assistant resident medical officers, house physicians, resident and nonresident porters, pathologic assistants and dispensers, in all 369 persons, of whom twelve, or 3.2 per cent., developed phthisis later, two of them through inoculation wounds.

The comments of Goring on this report are most interesting. He compares these results with those obtained by himself in a study of 3,090 individuals of nontuberculous parentage, assuming that a person coming of tainted stock would not be likely to take service in a consumptive hospital. Among his 3,090 persons, seventy-nine, or 2.6 per cent. developed tuberculosis. Thus two groups, one exposed to special risks and one not, showed an amount of infection varying only 0.6 per cent. If the two hospital cases, associated with inoculation wounds, are left out of consideration, we have practically the same percentage of infection, 2.6 and 2.7 per cent.

Since the foundation of the Adirondack Cottage Sanitarium, more than twenty-eight years ago, there

has been no case of infection among the employees, including waitresses, chambermaids and laundresses.

Infection through marriage may give some clue to the susceptibility of adults. Cornet says, "The number of cases of marriage infection, often of classical simplicity, runs up into the hundreds." His own study of 594 couples showed that in 23 per cent. both partners were tuberculous. He admits that the findings do not necessarily imply an etiologic relation between the cases. Cornet believes the actual cases run higher than the figures given indicate. Other observers place marital infection at from 3 to 12 per cent. Recent studies made according to modern statistical methods tend to throw doubt on the earlier work.<sup>1</sup>

The late E. G. Pope's study of this question failed to show definite proof of infection between married persons. His work has been reviewed by Karl Pearson, who says:

I may conclude in the slightly modified words of Mr. Pope: It would seem probable then (1) that there is some sensible but slight infection between married couples, (2) that this is largely obscured or forestalled by the fact of infection from outside sources, (3) that the liability to the infection depends on the presence of the necessary diathesis, (4) that assortative mating probably accounts for at least two thirds and infective action for not more than one third of the whole correlation observed in these cases. But the demonstration of this result depends on the acceptance of the inherited diathesis to be effective, and the existence of assortative mating of equal intensity in the case of want of mental balance must prevent dogmatism. In all future collection of statistics with regard both to marital infection and parental infection, it is most important that the age of husband and wife at marriage and the age at onset and death in both should be recorded. Age at onset and death of the parent, age of parent at birth of child and age at onset and death of child should also be recorded. It is only by such complete records that we shall ultimately be able to accurately apportion the action of infection, assortative mating and inheritance.

For real light on the problem of assortative mating of the tuberculous, we must wait till we have definite knowledge in each case of the family history of both husband and wife. If we find (1) that the marriage of two ultimately tuberculous persons took place before either were suspected of the disease, and (2) that there is in such cases a larger percentage of family histories of tuberculosis than in the case of nonmarried tuberculous individuals, we should have definite evidence of the assortative mating which seems probable. If, on the other hand, the percentage were smaller, we should have definite evidence for the infection theory.

The difficulty of determining the date of infection by the appearance of clinical symptoms has already been mentioned. As our ideas have been in the past largely drawn from clinical data, it is evident that there is need of some revision. How such data may mislead is evidenced by the statement of Goring<sup>2</sup>:

The mean age of onset for both sexes taken together is about 27—the standard deviation is about nine years. It follows from this that the ages between 14 and 45 may be looked on roughly as a danger zone for tuberculous infection. The modal value of age of onset is about 23, and this is the age when danger of infection is most intense, the danger diminishing fairly rapidly to the age of 14, and more gradually to the age of 45.

1. Prisons have been notorious for the many cases of consumption which developed among prisoners, and these figures have been used as demonstrating infection. I have purposely left these out of consideration in this paper because of the class of people affected. It is almost certain that the majority of these cases are simply instances of recrudescence of an infection which took place in early life. There is, at least, so much doubt concerning them that I have not considered the figures justifiable for use in this discussion.

2. Goring: *Studies in National Detioration*, V.

It seems certain that the early years of life are those in which tuberculous infection takes place in the great majority of cases, and primary infection of adults is much less frequent than formerly believed. Clinical histories cannot be relied on to determine the period of infection. It seems equally certain that infection of adults does occur, and that no age is exempt.

#### CONCLUSIONS

1. The evidence at hand indicates that in the majority of cases the respiratory tract is the route of infection in tuberculosis.
2. The alimentary tract is a frequent portal of entry for the tubercle bacillus.
3. The tubercle bacillus is able to pass through the intact mucous membrane of the alimentary tract without producing a lesion at the point of entrance. This takes place most readily during the digestion of fats.
4. The bacilli pass with the chyle through the lacteals and thoracic duct into the blood, which conveys them to the lungs, where they are retained largely by the filtering action of the tissues.
5. Infection through the alimentary tract is especially frequent in children.
6. Infancy and childhood are preeminently the periods of life when the individual is susceptible to tuberculous infection, and the majority of cases of infection occur during these early years.
7. Any campaign against tuberculosis which leaves out of consideration the protection of children against infection will fail of success.
8. Tuberculous infection in adult life occurs, but not so frequently or readily as generally believed.
9. Tuberculous infection may occur at any age.

#### TRANSFUSION OF BLOOD WITH SPECIAL REFERENCE TO THE USE OF ANTICOAGULANTS\*

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NEW YORK

We previously reported<sup>1</sup> a method of transfusing blood by means of specially constructed pipets and canulas designed for use with either a lining of hardened paraffin or a preliminary internal coating of an anticoagulant solution such as leech extract or herudin<sup>2</sup>. During the past eighteen months we have experimented with various anticoagulants other than paraffin and herudin, with a view to determining the best anticoagulative agents for purposes of transfusion. We desire here to report the results of these experimental transfusions and to summarize the theoretical and practical advantages of the anticoagulants which we have studied; and in order to make more evident at the outset the practical bearing of this study, we propose, first, to discuss briefly the present status of blood transfusion as a rational therapeutic procedure, and to call attention to certain aspects of this problem which are not usually taken into consideration. It is not our

intention by this discussion to disparage the valuable and often brilliant results which have been and are being constantly achieved by blood transfusion, nor to argue for any special restriction of its field of usefulness, but we do wish to point out the need for a more exact knowledge of the biologic processes which are involved in transfusion of blood (or which may be involved under special conditions) in order that the certainty of its usefulness may be increased and that the liability to any untoward results may be minimized beyond what is realized at the present time.

In the constantly enlarging field in which transfusion of the blood is being employed, the questions which arise concerning the indications and contra-indications for this operation, the amount of new blood to be supplied, and the advisability of removing some of the patient's own blood at the time of transfusion, are all matters closely concerned with the probable benefit or futility of the operation. For instance, in the emergency of acute hemorrhage occurring in an otherwise healthy subject, or following the artificial removal of acutely poisoned blood, as in the treatment of gas poisoning, we believe that the problem is a comparatively simple one and that the established tests for hemolysis and agglutination between prospective donor and recipient are probably adequate, if indeed the urgency of the conditions may not make it imperative to proceed without taking time for even these tests. But the problem is far more complex when it is a question of the benefit to be derived from the transfusion of a so-called "normal" blood into the circulation of a patient suffering from one or more of the various pathologic conditions for which transfusion has been recommended, and we believe that this question could be more satisfactorily answered if laboratory methods were available for the detection of other possible grounds of incompatibility than those which are covered by the tests which are now in use.

Among the recent contributions to the literature of transfusion we can find only one reference<sup>3</sup> to accidents which appear definitely to suggest inadequacy of the present tests for blood compatibility, although there are numerous citations of unexplained chills and febrile reactions.

Percy<sup>4</sup>, in a series of fifty-four transfusions, met with toxic reactions in three cases in which the hemolysis and agglutination tests were perfectly negative, and two of these cases resulted fatally.

Ottenberg and Kaliski<sup>5</sup> estimated that there are toxic reactions not referable to hemolysis or agglutination, in 10 per cent. of all cases of transfusion, which estimate appears to be based on their own series of 128 cases.

Ottenberg and Libman,<sup>6</sup> in their series of 212 transfusions on 189 cases collected from hospital and private sources and performed by a number of different surgeons, have contributed a valuable classified report. These authors, in summarizing the untoward results due to transfusion, assign the most unfavorable reactions of their series, including five fatalities, to "incompatible blood" (meaning, apparently, hemolysis or agglutination only) or to hypertransfusion. But they also state that a "more or less febrile reaction" occurred in about 10 per cent. of all cases and that skin eruptions, usually urticarial, occasionally petechial, appeared in another 10 per cent. In referring to the hemolytic and agglutinative reactions as being an insufficient guide to the value of a given donor's blood for the purpose of stimulating a remission of the disease in pernicious anemia, Ottenberg and Libman

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1. Satterlee and Hooker: Surg., Gynec. and Obst., 1914, xix, 235.

2. Satterlee, H. S., and Hooker, R. S.: The Use of Herudin in the Transfusion of Blood, THE JOURNAL A. M. A., June 6, 1914, p. 1781.

3. Percy: Surg., Gynec. and Obst., 1915, xxi, 360.

4. Ottenberg, Reuben, and Kaliski, David J.: Accidents in Transfusion, THE JOURNAL A. M. A., Dec. 13, 1913, p. 2138.

5. Ottenberg and Libman: Am. Jour. Med. Sc., 1915, xl, 36.