Progress report on the investigation of pellagra / by Louis W. Sambon.

Progress Report on the Investigation of Pellagra

By LOUIS W. SAMBON, M.D., F.Z.S.

Lecturer to the London School of Tropical Medicine.

[Reprinted from the "Journal of Tropical Medicine and Hygiene."]

London

JOHN BALE, SONS & DANIELSSON, Limited

OXFORD HOUSE

83-91, Great Titchfield Street, Oxford Street, W.

1910

PROGRESS REPORT ON THE INVESTIGATION OF PELLAGRA.

By Louis W. Sambon, M.D., F.Z.S.
Lecturer to the London School of Tropical Medicine.

To the Pellagra Investigation Committee, London.

Gentlemen,—I have the honour to report the results obtained during the first three months of investigation carried out in Italy for the purpose of elucidating the etiology of pellagra. A fuller and more elaborate report will follow in due course at the conclusion of the work.

So far I have been able to establish :—

(1) That pellagra is not due to the eating of maize, either sound or deteriorated, as hitherto almost universally believed.

(2) That it has a striking, peculiar, and well-defined topographical distribution.

(3) That its endemic foci or "stations" have remained exactly the same in many places for at least a century.

(4) That its stations are closely associated with streams of running water.

(5) That a minute blood-sucking fly, of the genus *Simulium*, is, in all probability, the agent by which pellagra is conveyed.

I regret that, so far, circumstances have not permitted me to attempt the necessary experimental work to actually and completely prove the agency of *Simulium* in the transmission of the disease; but I believe that I have brought together a body of evidence sufficiently powerful to render it almost a certainty.

Researches made for the purpose of discovering any protozoal or other parasite that might be regarded as

the causative agent of the disease have so far met with a negative result; but it must be pointed out that such researches necessarily have been very limited, the short period of work having been mainly devoted to the study of distribution and epidemiology.

Several original observations on the historical, clinical, and epidemiological aspects of the disease, as also on the bionomics of the *Simuliidæ*, will be found briefly mentioned in this report.

In 1905, at the Leicester meeting of the British Medical Association, I stated my belief that pellagra was an insect-borne parasitic disease, and that the specific parasite might possibly be a protozoal organism. This year, at a meeting of the Pellagra Investigation Committee, held at Dr. Cantlie's house on January 21, I suggested that the transmitting agent might be a *Simulium*.

My hypothesis was founded on topographical and epidemiological facts, partly observed by myself, partly gathered from literature. In 1900 and 1903 I had visited some of the pellagra-affected districts of Northern Italy, and, in preparing my lectures for the London School of Tropical Medicine, I had read many of the older Italian works on the disease, such as those of Frapolli, Albera, Odoardi, Fanzago, Sartogo, Cerri, Chiarugi, and Gaetano Strambio, sen., which contain very valuable information.

The recent investigation carried out on behalf of this Committee substantiates my suggestions, and, in my opinion, demonstrates the reliability of topographical and epidemiological data when correctly interpreted. In 1903, availing myself of similar data, I was able to infer that sleeping sickness is a tsetse-borne disease, and to indicate the very species of the carrier —*Glossina palpalis*—conclusions which subsequent investigations in Africa have fully established.

This spring my investigations on pellagra were again pursued in Italy, in the provinces of Milan, Bergamo, Brescia, Padua, Rome, and Perugia.

Acknowledgments.

During the first six weeks I had the valuable co-operation of Dr. J. F. Siler, Captain Medical Corps, United States Army; Dr. Triade Perico, of Bergamo; Mr. Ugo Baldini, and Mr. Edward de Ville. In the course of the last six weeks I had the great advantage of being joined in my researches by Dr. C. H. Lavinder, Passed Assistant Surgeon, and Dr. Rupert Blue, both of the United States Public Health and Marine Hospital Service, who had been detailed to investigate pellagra in Europe. Throughout I had the help of Mr. Arthur Amoruso, who acted principally as field naturalist.

In each province the "medico provinciale," or chief medical officer, indicated the affected districts, and usually joined me in my excursions. In each district I was invariably accompanied by the "ufficiale sanitario," or district health officer, whose knowledge of the local conditions proved most valuable.

Dr. Pizzini, the Municipal Health Officer of the town of Bergamo; Dr. Randi, the Municipal Health Officer of Padua; Professor Pisenti, of the University of Perugia; Dr. Betti, Director of the Hospital of Città di Castello; Professor Stefani, President of the Pellagra Commission of the Province of Padua; and Mr. Panin, the Pellagrological Inspector for the Province of Padua, also accompanied me in several of my excursions within their respective areas.

In each province I visited the local insane asylums, hospitals, "pellagrosari, locande sanitarie," schools, and other institutions. Everywhere I made it a point of getting in touch with those who had devoted special attention to the study of pellagra. Thus I had very interesting and instructive discussions with the Marquis Patrizi, Professors Marzocchi, Antonini, Gosio, Celli, Belmondo, Pampana, Agostini, Terni, Pavone, Tamburini, Badaloni, Devoto, Frosini; Doctors Tiraboschi, Fabbri, Fritz, Ceresoli, Gemelli, Bezzola, Peroncito, Mariani, and many others.

Amongst those who most contributed to the success of my investigation, I must particularly mention Drs. Lavinder and Siler, both of whom had previously studied the disease in the United States of America; Professor Balp, Chief Medical Officer of the province of Bergamo, Prof. Centonze, Chief Medical Officer of the province of Perugia; Professor Pisenti, of the University of Perugia; Dr. Perico, of Bergamo; Drs. Betti and Sediari, of Città di Castello; Dr. Coluzzi, of Ponte Pattoli, and Dr. Magnini, of Deruta.

I take this opportunity to express my appreciation of many courtesies received, and my especial indebtedness to His Excellency Sir Rennell Rodd, British Ambassador in Rome; to His Excellency the Marquis of San Giuliano, Italian Minister for Foreign Affairs; to Commendatore Santoliquido, Director-General of Sanitation in Italy; to Count Suardi; to Commendatore Mario Mancini; to the Mayors of Bergamo, Padua, Perugia, Città di Castello, and Citerna; and to the Pellagra Commissions of Bergamo, Padua, and Perugia, for the many facilities afforded me in my researches.

Present Italian Theories concerning the Etiology of Pellagra.

The theories on the etiology of pellagra which I found to be now held in Italy are the following:—

(1) Insufficiency of nutriment owing to poverty, inappropriate food (maize), and lack of wine.

(2) Toxicity of maize, especially when used exclusively as an article of diet.

(*a*) Owing to specific toxic substances normal to this cereal, even when of good quality and perfectly sound.

(*b*) Owing to toxic substances produced at spring time, during the process of germination.

(*c*) Owing to toxic substances resulting from the action of *Bacillus coli* on sound maize, within the alimentary canal, after ingestion.

(*d*) Owing to toxic substances elaborated during the decomposition of maize.

(i.) By the common blue mould, *Penicillium glaucum*.

(ii.) By certain particular strains of *P. glaucum*.

(iii.) By several kinds of fungi and bacteria.

(3) Parasitism of certain organisms ingested with either sound or deteriorated maize.

(*a*) Certain fungi: *Aspergillus fumigatus* and *A. flavescens*.

(*b*) *Streptobacillus pellagræ*, an organism which Professor Tizzoni claims to have isolated from the blood, cerebrospinal fluid, tissues and fæces of pellagrins, as well as from damaged maize.

(4) Parasitism of a nematode worm, belonging to the family *Filariidæ*, which Professor Alessandrini claims to have found in the skin of pellagrins and in the the drinking water of affected districts.

With the exception of the last-mentioned hypothesis, only quite recently enunciated (May, 1910) by Professor Alessandrini, all the prevailing theories agree in making maize responsible for the incidence of the disease, notwithstanding that they are all greatly at variance with regard to the mode of action of the assumed cause.

The belief in a relationship of cause and effect between maize and pellagra is based chiefly on the following *assumptions*:—

(1) The disease appeared for the first time in Europe soon after the introduction of maize from America.

(2) It followed everywhere the extension of maize cultivation, and increased *pari passu* with the more general adoption of the new cereal as an article of food.

(3) It occured only in places in which maize is either grown or imported, and exclusively in people who use it as an article of food.

Credence in the maize theory is further supported by the generally accepted statement that the disease

has greatly diminished both in prevalence and severity, owing to the adoption of various preventive measures, all based upon this theory, and all equally concerned in eliminating maize from human consumption. The measures adopted are :—

(1) The inspection of maize, and seizure of all unsound grain and its products.

(2) The exchange of deteriorated maize for good maize.

(3) The providing of drying apparatus for damp maize.

(4) The providing of suitable bakehouses in rural districts for the proper baking of maize bread.

(5) The abolition of late varieties of maize which do not ripen properly.

(6) The compulsory notification of all cases of pellagra.

(7) The obligation, in all affected districts, upon the municipal authorities to supply free meals to all their pellagrins twice every year for periods of not less than forty days.

(8) The institution of special retreats, "pellagrosari," for the housing, feeding, and treatment of the more advanced cases.

(9) The dispensation of free salt to all pellagrins and their families.

Objections to the prevailing Italian Theories.

All theories making maize the direct causative factor of the disease are opposed by the following *facts* :—

(1) There is no foundation whatever for the belief that pellagra broke out in Europe soon after the introduction of maize from America.

(2) The topographical distribution of pellagra does not coincide either with the distribution of maize cultivation or with that of maize consumption.

(3) The disease occurs frequently in persons who have seldom or never partaken of maize as an article of food.

(4) All preventive measures based on the maize theory have failed.

(5) The characteristic skin eruption and other symptoms of the disease may recur each spring for several successive years in patients who are far removed from the endemic districts and who abstain from maize.

Origin of Pellagra.

We have no reliable historical evidence to prove that pellagra existed in Europe before the eighteenth century, when Casal and Frapolli recognized it to be a distinct morbid entity. Neither have we any definite evidence, however, to show that it had only just appeared when first described by these authors. I will endeavour to show that the universal belief which ascribes the first outbreak of pellagra in Italy to the middle of the eighteenth century is wrong, and that the disease must have existed centuries before.

The earlier Italian physicians who wrote about pellagra state that the disease had long been known in their respective districts, not only to practitioners, but to the very peasants, who had, in each place, a particular name for it. Thus the term pellagra, now universally adopted, was not coined by Frapolli, who, by the way, spelt it wrongly (pelagra), but was the popular name of the disease in Lombardy, just as "salso," "mal rosso," "pellarina," "mal della spienza," "mal del padrone," were in various other parts of Italy. Frapolli (1771) asserts that the disease is "as old as the sun," and considering the term "pallarella" to be a synonym of pellagra, he mentions an order issued by the Ospedale Maggiore of Milan on May 6, 1578, in which it is stated: Article 5, That those suffering from pallarella, crusts, gummata, and sores, be admitted, provided they have the order undersigned as above." Odoardi (1776) informs us that the disease had been observed by Professor Giuseppe Antonio Pujati when practising in Feltre (about 1740), and by Drs. Nascimbeni and Anton-Gaetano Pujati in Friuli,

but that until then no one had described it, probably on account of its being overlooked, the malady occurring in mountainous districts where good physicians are seldom found. Albera (1784) says: "I believe that many diseases usually looked upon as new existed already in ancient times, and among them the one we are about to describe, with the only difference of the name, and of the severity of the symptoms, with which it now affects the greater part of the Milanese territory." And he adds: "Our oldest peasants state that already their ancestors spoke of 'mal rosso' and 'mal della rosa' as a disease presenting the early symptoms of our pellagra. Even now they use the same names to indicate its early stages, calling it pellagra when further advanced, and exhibiting the internal symptoms."

An important reason why pellagra was not described sooner is that it was confounded with other diseases, such as eczema, leprosy, erysipelas, and scurvy. Pujati, who first established the presence of pellagra in Venetian territory where scurvy was common, named it "Alpine scurvy." Odoardi retains this name because, he says, the two diseases have a common cause, produce like effects, and are cured by the same remedies. Sartogo (1791) called it "mountain scurvy," and Aldalli (1791) "scorbutic paralysis." Facheris (1804) states that, in the Department of the River Serio, pellagra was popularly known by the name of "scurvy," and that this denomination had continued, notwithstanding the great difference between scurvy and pellagra which he had pointed out in 1791. Marzari (1810) proposes the name of "Italic scurvy," and states that in the Department of Treviso this disease had always been called scurvy by the most accredited physicians, and was known to the peasants themselves by the corrupted term of "scoro-butto." In his treatise on scurvy, Della Bona obviously alludes to pellagra when he says: "*Interdum, sed rarius apud nos cutis finditur, asperi*

tudinemque habet, et squamas quasdam remittit sic ut ad eum morbum accedat quam graeci elephantiasim vocant." According to Facheris and others, Giuseppe Pasta, a famous physician of Bergamo, alluded to pellagra when, under the term Scurvy, he (1769) wrote: "A disease known and become familiar also in our regions."

The previous non-recognition of this disorder is by no means surprising. The history of many other diseases in this respect is similar to that of pellagra. It would be idle to seek for descriptions of typhoid fever in the medical writings of antiquity or of the Middle Ages, and yet this disease was no new malady when definitely extricated in the eighteenth century from the old "febres pestilentes." The history of rickets is just as obscure prior to Whistler's thesis (1645) and Glisson's famous treatise; yet it would be a great mistake to believe that the so-called "morbus puerorum Anglorum" appeared as a new disease at the beginning of the seventeenth century and broke out for the first time in the English counties of Dorset and Somerset. Scarlet fever was not recognized as a distinct disease before the seventeenth century, when the works of Sennert, Doering, and Sydenham crystallized the medical comprehension of this morbid process. It would be absurd to believe in any of the dates assigned to the first appearance of this disease in the various European States. In all probability it had long existed, but had always been confounded with measles. Scurvy is another disease the history of which does not go further back than the fifteenth century, when it was brought prominently to notice by the havoc it played aboard ship: as in Vasco de Gama's great voyage round the Cape in the year 1497, when 100 out of a total of 160 men succumbed to it. Until a few years ago kala-azar was looked upon as a disease peculiar to Assam. The discovery of its causative agent by Sir William Leishman, in 1903, made the diagnosis comparatively easy, and the

disease was soon reported from Ceylon, China, North Africa, Sicily, and other parts. Its late recognition in these places, however, does not in any way signify recent importation.

Returning to pellagra, it is interesting to notice that the disease was recognized in Egypt by Pruner as early as 1847; but Pruner's statements were discredited by Hirsch, and almost half a century elapsed before it was definitely proved, by Dr. Sandwith's investigations, that pellagra is one of the scourges of Egypt, and a very serious one among the Fellaheen of the lower country. The case of the United States of America is again most instructive. Until quite recently all American text-books stated quite emphatically that pellagra was unknown in that part of the world; then suddenly the disease is discovered in no fewer than twenty-six States. This wide distribution of the disease; the diagnosis of a few cases as early as 1863 or 1864 in the New York and Massachusetts asylums; and the absence of any definite history of recent importation or outbreak; show very clearly that the disease is of long standing in the United States: yet it escaped recognition.

A fact which powerfully suggests that pellagra could not have appeared for the first time in Italy about the middle of the eighteenth century, but that it must have been far more ancient, is the wide distribution it had already attained at that time. Indeed, we know that it ranged throughout the North of Italy from the Julian Alps to the Alps of Piedmont, from Lago Maggiore to the Arno. I have already mentioned that Pujati saw the disease at Feltre about 1740, and that Nascimbeni a few years later recognized it in Friuli. Soler (1791) found it along the River Piave in the district of S. Polo, Sartogo (mentioned by Fanzago, 1791) in the neighbourhood of Aviano, Aldalli (mentioned by Soler, 1791) near Sarone, a village at the foot of the Julian Alps. Fanzago (1804) states that Dr. Storni, who practised for over forty years in

Campo S. Piero, Padua had never observed any difference either in the number of persons attacked or in the severity of the disease. He believed that the malady could not be looked upon as of recent origin, since his predecessor, Dr. Carlo Barbanti, who had taken up residence in that district thirty years before him (about 1730) had stated that he had always observed it in those places. A work published in Naples in 1788 ("De epidemicis et contagiosi morbis") mentions the existence of pellagra in the territory of Modena. Tarzaghi (1794) states that the disease had been noticed previous to 1730 in the vicinity of Sesto Calende (on Lago Maggiore); Albera (1781) says: "Dr. Bava, a man of repute and learning, has told me that pellagra had been known for over sixty years (1720) in the Ligurian mountains; it proceeded in the same order, and manifested itself and grew with the same symptoms. It was ascribed by the local physicians to the moist heat of the stables in winter. They did not, however, describe it, and withheld from posterity the cure." Allioni (1795) mentions its early existence in Piedmont, and Chiarugi (1814) states that Dr. Vincenzo Tozzini recognized pellagra in the Valley of the Mugello as early as 1784, and that in 1798 his observations had been confirmed by a diligent and learned surgeon, Signor Giuseppe Targetti. Chiarugi describes the disease as widely distributed throughout Tuscany. He says: "The carefully kept registers of our hospital show that, besides being very prevalent in Mugello, the disease we are examining is also found at Bagno, and at Marradi, in the Romagna Toscana; at the Filigare on the Bolognese frontier; at Incisa in the upper Valdarno; at Ponte a Sieve; and at the Ambrogiana; in the Valley of Nievole; in the upper district of Prato at Usella; on the very Poggi near to us (Florence), of Bivilgliano to the north; of the Romola, and Giogoli to the south; and finally in Florence itself, as we shall see further on. This coincides with the opinion of

certain physicians in the agricultural districts, who believe to have observed it in other parts of Tuscany." And further he says : "I remember now to have seen, more than twenty years ago, in our hospital a lunatic who presented at that time a desquamation unknown to me, which his relatives ascribed to sunburn ; this prevented my recognizing him as a pellagrin, which he certainly was. Moreover, at this moment we have among our pellagrins a certain Diamante Gressi, of S. Piero, in Bagno, who, about fifteen years ago, was treated by me with those affected by cutaneous diseases, as I believed her to be a leper, and who has remained up to this year free from any cutaneous affection or any other symptom of pellagra. The deep fissures and the pellagrous desquamation which she exhibited at that time are still present in my mind, and I now recognize that it was a case of true pellagra. She remembers everything, and, above all, the great lassitude which she experienced at that time, and which she feels now that she is once more attacked by the same disease."

Although pellagra was described by numerous physicians in various parts of Italy soon after Frapolli drew attention to it in 1771, and although no one had ever mentioned it before in any part of the peninsula, it would be a mistake to believe that the disease had suddenly broken out in the neighbourhood of Milan, and was rapidly extending its domain. This would have been a mode of diffusion unknown to it. It seems, therefore, more reasonable to suppose that, enlightened by Frapolli's paper, many physicians were prompted to make known the observations they had already made on this disease in their respective districts, and that others were induced to look for it among their patients. Thus the wide distribution and great prevalence of the disease in Italy was soon broadly outlined. Such is the twice-told tale of most diseases.

A sudden influx of literature on a newly described disease is not necessarily an indication of recent ap-

pearance or unusual prevalence. Speaking of typhoid fever, Hirsch says: "This large amount of writing on typhoid, especially between 1830 and 1840, has given rise to the often-expressed opinion, which at one time I shared, that we have to do with an unusually general prevalence of the disease during that period, or that its general diffusion had not been reached until recent times. I think, however, that we must consider this to be an erroneous view, and that we must explain the phenomenal outburst of literature by the sudden and rapidly culminating interest of the profession in a new and important object of study—a phenomenon which has recurred in the case of many other forms of disease."

The sudden flood of American literature on pellagra and the recognition of the disease throughout the greater part of the United States, since 1908, when Dr. J. W. Babcock inculcated its grave importance, are but a repetition of what happened in Italy at the close of the eighteenth century.

Assumed Connection with the Introduction of Maize.

With regard to the introduction of maize into Europe, I believe there is little doubt that it was brought over by the Spaniards from South America, soon after the discovery of the Columbian Continent. The various documents brought forward to prove an earlier importation from Asia, such as that of Incisa, published by Molinari in 1810, are looked upon by the most competent authorities as of very doubtful authenticity.

We have no definite information as to the date of the introduction of maize into Italy, but a perusal of old Italian books on foods and cookery has enabled me to gather sufficient information to show that "melega," "melica," or "formentone," as maize was called, was used as an article of food as early as the middle of the sixteenth century.

Savonarola, in his book on foods published in 1554,

states that the bread made of "melega" is less nourishing than that made with any other kind of grain, and is of difficult digestion. Bartolomeo Boldo, in his revised and amplified edition of Savonarola's work, published in 1576, adds that "melica," "melega," or "milio indico" is made into bread by the peasants in time of scarcity, but is sown chiefly for the purpose of feeding fowls, pigeons, and other animals. Antonio Frugoli in his "Practice of Carving," published in 1638, mentions numerous ways in which maize may be prepared for the table, as "polenta," bread, pies, and tarts. "For the confection of tarts the maize meal should be cooked in milk or in a good, fat stock, then mixed with beaten eggs, grated cheese, sugar, and cinnamon." He says: "Formentone is called by some Turkish, but in reality it comes from the West Indies, and there are four kinds, according to the colour of the grain, because some are red, others black, yellow, or whitish, although it all belongs to one species; and it is found in various parts of Italy, particularly at Ferrara and in the towns of Lombardy."

From authentic documents of the time we learn that "melica" or "formentone" was grown in Cremona in the sixteenth century, and Professor Robolotti found that in 1556 a Cremona nobleman offered the Duke of Florence 10 staia of the new cereal for the purpose of sowing it in Tuscany. Zanon, in his work on "Agriculture and the Arts," states that maize was unknown in Bologna before 1600, and in Friuli before 1610. According to Marzari the first document mentioning maize in Treviso is dated January 16, 1686. Facheris states that in the territory of Bergamo maize was first grown in the Gandino district in 1632.

The above references show that maize was grown and used as an article of diet in Italy no less than a century and a half, and in some parts, two centuries before the date usually assigned to the

appearance of pellagra. It is impossible, therefore, to connect the introduction of the new cereal into Italy with the first appearance of the disease in any definite or reasonable manner.

To maintain that pellagra advanced *pari passu* with the extension of maize cultivation and with the more general adoption of this grain as an article of food, is, I consider, as gratuitous an assertion as that concerning its first appearance in connection with the introduction of maize.

Pellagra in People who do not eat Maize.

That pellagra affects only those who feed on maize is contrary to ascertained facts. The disease has been observed repeatedly in places where maize is neither grown nor eaten, and in persons who have seldom or never partaken of it. At a meeting of the Catalonian Academy of Medicine, Casana stated that in Spain the sad boast of the greater prevalence of pellagra belonged to those provinces in which the use and cultivation of maize were unknown.

Without here recalling the numberless instances reported at various times from Spain, France, and other pellagra-affected countries, I will mention some recent Italian examples.

Dr. Conti, Chief Medical Officer of the Province of Ravenna, states that pellagra is not confined to the small mountainous region in which maize is eaten, but that it occurs also in the district of Lugo, where maize is not used. Doubting whether these cases were genuine pellagra he suggested a revision of the diagnosis with Gosio's methods, not excluding the test with specific precipitines.

In 1903, Dr. Guido Garbini described five typical cases of pellagra under the name of pseudo-pellagra, because they occurred in the lunatic asylum of Messina in people who had never eaten maize. Dr. Garbini says: "Although all the symptoms indicate pellagra, in view of our present knowledge concern-

ing its etiological factors we cannot consider our patients to be pellagrins. The entire absence of the etiological element of pellagra, as also the fact that they are not the progeny of pellagrins dissuade us from forming such a diagnosis and confirms us in the belief that the dread disease does not exist in Sicily. It is a well-known fact that in this island maize is neither grown nor imported from abroad for local consumption, since it is neither eaten in the form of polenta nor in that of bread. Only very exceptionally it is eaten grilled on a charcoal fire. The Sicilians, says Tonini, may be extremely poor, indeed they may live solely on the parings of prickly pears, but they will never eat maize, which is totally unknown to the majority of them. It might be suggested that what is not done by all might be done by a few for special reasons. This, however, is not admissible in the case of our patients because for several years they had lived in the asylum, and through information obtained both from their respective families and themselves we learnt in the most positive manner that they had never eaten maize.

"Nor can the opponents of the maize theory, if there be still any, avail themselves of these five cases of mine to breathe new life into the inanition theory, because it will suffice that I point out that our patients had already been a long time in the asylum where the food has always been plentiful and of good quality, and that even before admission, though poor, they had never suffered from starvation. On the other hand, since we are unable to ascribe the erythema to the use of alcohol, on account of the time they had been in the asylum and because they had always been abstemious before admission, we are led to the conclusion that our patients are suffering from that form of chronic dermatitis which A. Bianchi, among others, believes to be due to the sun's rays, and which he has observed in demented and imbeciles, and which, indeed, is called pellagra or pseudo-pellagra of the insane."

Cases of pellagrins who have seldom or never eaten maize are by no means uncommon in Italy. Two such were recorded quite recently by Professor Mondini, of Genova. In neither of them could maize derived alcohol account for the disease, as both were abstainers.

During my recent investigation, in almost every district I have been told of trustworthy cases by the local health officers. Some of these cases I have myself examined.

In Rome Professor Tamburini, the eminent Italian psychiatrist, showed Dr. Lavinder and myself a case in his clinical wards which, he pointed out, was of special interest, because it was the first case so far reported from Rocca Priora, a mountain village within the Roman territory, and because maize could not be considered a factor in its causation. The patient, Arcangelo Teofani, a man of about 60 years of age, was a typical pellagrin. Dr. Bonfiglio, clinical assistant to Professor Tamburini, informed me that there was no history of syphilis or alcohol in the case. The characteristic erythema had two years ago appeared for the first time; there was mental confusion, marked paresis, and rigidity of trunk and limbs. The patient had worked in the fields, but his economic conditions were comparatively excellent. In his family, composed of wife and four children (three boys and one girl), during the winter months polenta was eaten about twice or three times in the week, but he had never touched it, and ate only wheaten bread, although the others partook of maize bread. His wife and children, notwithstanding the amount of maize they consumed, were perfectly healthy. They had never exhibited any symptoms of pellagra.

At Torgiano (Assisi) the District Health Officer, Dr. Giovanni Severi, mentioned the family Sforna, composed of eleven members, all pellagrins. These people own a considerable amount of land and are in very good circumstances. They seldom eat maize,

and then only of the very best quality. They live in a place called Brufa, close to the Chiogio, a confluent of the upper Tiber.

Dr. Severi also mentioned a man called Angelo Foricchi, who died of pellagra in Torgiano, notwithstanding that he had "never eaten a single grain of maize."

At Deruta (Assisi), Drs. Magnini and Lupatelli both mentioned the case of Achille Saracchi, a typical pellagrin, who lived at Ponte Nuovo, near Deruta, and asserted that he had never eaten maize.

Dr. Magnini introduced Dr. Lavinder, Prof. Centonze, Professor Pisenti, and myself to Signor Costanzo Boccali, Municipal Councillor of Deruta, who, five years ago, had suddenly presented marked pellagra erythema on the back of his hands. The eruption had occurred each spring in three consecutive years, but had finally yielded to arsenical treatment. Signor Boccali, an exceedingly pleasant and cultured gentleman, told us that the majority of physicians *would* not diagnose pellagra in his case on account of his social position and circumstances, but he knew perfectly well himself that the disease he was suffering from was the very same he had so frequently observed in the peasants of his district.

At Ponte Nuovo, with Drs. Magnini and Lupatelli, I examined Giuseppe Isidori, a man aged 43, a pellagrin of five years standing, who stated that he had not eaten any maize for the last eight or ten years.

At the same place I was shown Assunta Brumesi, aged 55, a pellagrin who had seldom eaten maize. This woman carried in her arms her daughter's son, Ferdinando Spera, a child 18 months old, and which presented marked pellagrous erythema on hands and face, although it had never touched maize and was only just weaned.

At Bastia (Perugia) the District Health Officer, Dr. Ettore Palombi, mentioned the case of Ottavia

Antonelli, who died of pellagra at the age of 50. This woman had not eaten maize for at least five years before her death.

He also mentioned the case of Maria Tini, a wealthy landowner, who, owing to pellagrous insanity, committed suicide by drowning herself in the river Chiagio. He believed she had never eaten maize, though of this he was not quite certain.

At Nocera Umbra, Dr. Fattore told me of two new cases of pellagra, notified the day previous to that of my visit by his colleague, Dr. Giuseppe Rossi. Both cases belonged to the family Rambotti, of Colle, one of the wealthiest in the district. Neither of the two patients had ever eaten maize.

Dr. Fattore also mentioned the case of Luigi Micciani, aged 65, who lived on his own land at a place called "Micciani." This person was a genuine pellagrin, though he had never eaten maize.

At Città di Castello, Drs. Fabbri and Tellarini mentioned the case of a woman, by name Gambuli, a wealthy landowner, who was treated for some time in the Pellagrosario Umbro, and who asserted in the most emphatic manner that she had never eaten maize.

Dr. Lignani, Medical Officer of S. Giustino, told me that Don Antonio Lucari, Archpriest of Morra, was a confirmed pellagrin, notwithstanding that he fed well and never ate maize.

Dr. Lignani also mentioned a certain Adriano Andreani, of Lugnano, a well-to-do pellagrin, who had seldom, if ever, touched maize.

At Morra, Paradiso, and other localities, I came across a number of pellagrin children, varying in age between 5 and 12 months, whose mothers asserted that the infants had never tasted maize, although they had often been given little paps of wheat flour, and sometimes a few drops of wine to regulate their bowels.

At S. Giustino Dr. Antonio Ferri mentioned a pellagrin from Citerna, called Rossi, who worked for

the Marquis Bufalini, was in good circumstances, and asserted that he never ate maize.

Dr. Ferri told me also of two other pellagrins who had never eaten maize : Domenico Baldelli, a peasant, in the service of Baron Leopoldo Franchetti, and Signor Valenti, brother of the Archpriest of S. Giustino.

At Citerna, Dr. Gallo Galletti told me that the gravest case of pellagra he had ever seen was that of a man who said he had never eaten maize, a certain Giorgi, belonging to a wealthy family of S. Pietro a Monte.

At Bergamo, Dr. Minelli, Bacteriologist to the Ospedale Maggiore, told me of a typical case he had seen in a young lady of good family. The skin lesions and other symptoms were quite characteristic, but for a long time the diagnosis had been doubtful on account of her social condition and food habits.

I have mentioned only the cases I was able to examine myself, and a few of those reported by the district health officers with whom I had the opportunity of conversing, but, no doubt, a special investigation throughout the pellagra districts of Italy would bring to notice hundreds of well-authenticated cases. I am quite prepared to admit that in certain instances the statement of *never* having eaten maize may not be absolutely true, but such a possibility cannot be looked upon as a proof of the worthlessness of all the cases ever mentioned, and, besides, an occasional meal of polenta does not invalidate even those cases in which it can be proved, else we should have to admit that even a few mouthfuls of polenta would suffice to cause pellagra, a proposition which even the most intolerant zeists would consider absurd. Of this I am certain, because with several of the latter I discussed the subject over a Brobdingnagian dish of the national polenta.

It is curious to notice with what extraordinary

tenaciousness the Lombrosian zeists have endeavoured to put aside any evidence that might prove the occurrence of pellagra in persons who have seldom or never partaken of maize.

Dr. Alpago-Novello, in reviewing for the *Rivista Pellagrologica Italiana* of July, 1907, a report by Masi, Tambroni, and Baldassari on "Pellagra in the Province of Ferrara in 1906," says: "One thing which has infinitely displeased me in this report bearing the name of Tambroni, whom I so greatly esteem, is the following extraordinary paragraph, which may be read on p. 6:—

"'We have also made the observation—probably of value in the elucidation of the etiological problem—that some individuals presenting evident symptoms of pellagra did not use maize flour.'"

"This is 'Spanish' pellagra, or, in other words, a perfect hoax!"

"But do they not see, the egregious writers of the report, that if their observations had been really true, all that is now believed by the universality of pellagrologists on the etiology of pellagra, a disease *inadmissible in the absence of maize*, would be entirely overturned? And I refer to all pellagrologists, including Masi, Tambroni, and Baldassari, who, in their report, and, indeed, on the very same p. 6, speak of fighting the maize intoxication. But what maize intoxication, if now they have discovered pellagrins who *never used maize flour?*"

Dr. Alpago-Novello's jocular expression "pellagra de Espana" refers to the fact that the great majority of Spanish physicians have never believed in the maize theory. Indeed, in 1867, the Royal Academy of Medicine of Madrid conferred a special prize on Dr. Calmarza for a work in which, in concurrence with the almost unanimous opinion of all Iberian investigators, he declares that the causation of pellagra cannot be ascribed to the eating of maize.

Failure of Preventive Measures.

The facts and arguments so far advanced already show very clearly that the maize theory is founded on very doubtful premises. However, as already stated, modern zeists claim that the remarkable success that has crowned the application of their prophylactic measures, based entirely upon the maize theory, is a most telling and irrefutable fact in favour of the correctness of this theory. It behoves us, therefore, to examine most carefully these preventive measures, study the reasons for which they were proposed, establish the exact time at which they were first adopted, and examine the way in which they have been applied and the results that are said to have been obtained in consequence of their application.

The case for the "zeists" cannot be put more authoritatively than in the words of Professor G. Sanarelli, Under-Secretary of State for Agriculture, who, in his opening address at the last Pellagra Congress (1909), said :—

"The beneficial results derived from the application of the law of 1902 became evident so soon that already in 1905, less than three years after its passing, the pellagrins within the kingdom were reduced to barely 55,000, showing a decrease of over 17,000 in the last six years!

"Until we have a new pellagrin census to confirm the increasingly progressive reduction of this social sore, which, fortunately for our country, is gradually healing, we must from this very moment draw the most auspicious omens from the continuous and marked decline of the death-rate due to pellagra within the last few years.

"Indeed, whereas in the three years, 1887-89, the victims of pellagra throughout the whole kingdom were 10,284, in the next three years, 1900-02, they fell to 9,218; in the three years following, 1903-05, they further declined to 7,367; and in the last three years, 1906-1908, they have fallen to 4,649 only.

"But there is something still more comforting. Whereas in 1907, 4,950 new cases were notified, last year only 2,824 were reported. Whereas before the application of the present law, the yearly pellagra mortality constantly reached, or even exceeded, the figure of 3,000, immediately after the year 1902 the number of deaths only just exceeded 2,000, in 1907 the deaths were 1,635, and last year they were reduced to about 1,000!

"Now, if on the basis of the last censuses of 1889 and 1905 we can reckon that about 24,000 notified pellagrins correspond to every thousand deaths from pellagra, we are bound to conclude that at present, within the whole kingdom, these unhappy beings do not exceed the number of 25,000.

"Therefore, the prophylactic and curative work carried out within the last three years has further reduced the number of pellagrins by more than 50 per cent.

"And this is a sure indication that the combined action of both the Government and the local bodies have attained decisively positive and greatly beneficial results."

Professor Sanarelli further stated that if the law of 1902 "had only been fully and vigorously enforced in all the forty-four provinces of the kingdom more or less severely affected by the fatal disease, at this hour the whole of Italy would be entirely free."

I will endeavour to show that the law of 1902, far from bringing about such "decisively positive and greatly beneficial results," has failed to produce any results at all. In doing so I earnestly hope that I shall not be misunderstood, my sole object being to arrive at a clear understanding of all such circumstances as may help in the elucidation of the true cause of pellagra.

In the first place, I must point out that if there has been any decline in the number of cases and deaths reported, such decline cannot reasonably be ascribed to the enactment of the law of 1902, because

the decline had already begun in a very striking manner several years before the framing of the law, and also because the law of 1902 did not come into force until three years later, and then only for some of its least important provisions. Indeed, to refute Professor Sanarelli's assertions I need but quote an earlier statement made by the same authority in the *Giornale della Reale Societa Italiana d'Igiene*, November 30, 1907. In that paper he says: "Notwithstanding the application of the law of July 21, 1902, for the prevention and cure of pellagra; notwithstanding the assiduous propagandism and the increasingly active endeavours of the Provincial Pellagra Commissions; notwithstanding the great subsidies made by the State; the locande sanitarie; the exchange for bad maize; the dispensation of free salt; the encouragements given for the promoting of wheat cultivation; the teaching of sound agrarian principles; and many other direct or indirect measures excogitated by private initiative and by the Government, to efficiently fight against pellagra; this disease in Italy does not show any tendency to decline in a satisfactory measure.

"It is true that in these last years the general death-rate from pellagra has gradually diminished, and that at first sight this marked improvement might appear to be due to the application of the law of 1902. But in comparing either the numbers of pellagrins or the numbers of deaths from pellagra in the three years, 1900-02—that is to say before the application of the law—with those of the three following years, 1903-05, one finds that all these figures do certainly indicate a gradual, progressive improvement, but an improvement which takes place in more or less the same proportions.

"A legitimate doubt therefore arises as to whether it be right to ascribe the gradual decline of pellagra throughout the kingdom to the measures contained in the law of 1902.

Years.	Deaths from Pellagra.	Pellagrins in the whole Kingdom.	
1898 ..	3,987		
1899 ..	3,836 ..	First census (1879)	97,855
1900 ..	3,788 ..	Second census (1881)	104,067
1901 ..	3,054 ..	Third census (1899)	72,603
1902 ..	2,376 ..	Fourth census (1905)	55,029
1903 ..	2,647		
1904 ..	2,363		
1905 ..	2,359		

"This decline was already in progress prior to the application of the law.

"Further, if instead of comparing the enumerations of pellagrins for the whole kingdom, we proceed to compare the numbers for the single regions such as they appear in the last three censuses of 1881, 1889, and 1905, we find: (1) That in two large regions of Central Italy—viz., Umbria and the Marche—pellagra has now become extraordinarily more diffused than it was twenty-five years ago; (2) that in Tuscany it also shows a tendency to extend more widely; (3) that in Latium and the Abruzzi, where in the past it seemed to be almost unknown, it is now showing itself in proportions which may become alarming.

	Number of Pellagrins Enumerated.		
Regions.	1881.	1889.	1905.
Piedmont	1,328 ..	1,223 ..	1,012
Liguria	56 ..	30 ..	56
Lombardy ..	36,630 ..	19,557 ..	15,746
Venitia	55,881 ..	39,882 ..	27,781
Emilia	7,891 ..	4,617 ..	3,357
Tuscany	924 ..	1,125 ..	1,137
Marche	406 ..	920 ..	1,436
Umbria	872 ..	5,103 ..	4,250
Latium	32 ..	146 ..	195
Abruzzi and Molise	— ..	— ..	—

"With regard to the other regions, and more especially Lombardy and Emilia in which the progressive decline of pellagra is truly remarkable, also as compared to the enumeration of 1881, one cannot exclude the intervention of new beneficial economic and social conditions known to all, which may have

influenced the sanitary conditions of their populations.

"These findings therefore seem to confirm what I have stated above, namely, that the present prophylactic measures against pellagra cannot be considered either sufficient or appropriate to stamp out in a definite way the maize poisoning."

Inspection of Maize and its Products.

In order to better ascertain the true preventive and curative value of the measures contemplated by the law of 1902, I propose to discuss each measure separately.

The inspection of maize and its products is obviously the most important measure, in view of the belief which ascribes pellagra to the toxic substances generated in deteriorated grain, but, to be of any practical use, it must lead to the seizure and destruction of all damaged grain.

As a means of prevention against the disease, the seizure of damaged maize is no new measure. Indeed, we can trace it back to November 22, 1776, when it appears to have been ordered for the first time by the sanitary authorities of the Venetian Republic, a few months after Odoardi had called attention to the prevalence of the disease in the Bellunese.

The Italian Government has at various times promulgated special orders concerning the abolition of damaged maize, but these orders have never been really enforced. Thus in September 1895, an order was published prohibiting the importation of damaged maize into the kingdom, but as stated by Badaloni (1902), the order gave rise to so much trouble that it had to be rendered practically useless by means of a circular dated October 15, 1895.

The law for the prevention and cure of pellagra of July 22, 1902, again prohibits the importation of unsound maize and provides for its seizure and

destruction or denaturation when the grain is intended to be used as human food, but it allows the introduction of damaged maize for feeding animals and for industrial purposes, thus offering many loopholes to unscrupulous speculators. And, indeed, it has been sold on the public markets labelled "for pigs," and the vendors stated that if men bought it for their own use that was no business of theirs; besides, were not men the greater pigs?

The enforcement of this law has not been attempted until quite recently (1907), and then only in a tentative and very insufficient manner. There are very serious difficulties which render its application almost hopeless. Amongst them are the necessity of importing from abroad large quantities of maize both for human food and for industrial purposes; the great pecuniary interests involved; the enormous amount of unavoidable deterioration which takes place in the grain during transit; the many technical difficulties concerning the proper demonstration of the degree of deterioration, especially in view of the fact that a certain amount of deterioration (5 per cent.) is officially tolerated.

This degree of deterioration tolerated by the Government, coupled with the unreliability of the methods available for the determination of the amount of deterioration, have not only frustrated the object of the law, but, as pointed out by Professor Balp (1908), have prompted millers to add 5 per cent. of damaged maize to all sound maize.

At the last Pellagra Congress (1909) Commendatore Cerutti proposed that the Government should be asked to withdraw its instructions relative to this toleration, but Professor Gosio pointed out that about half the amount of maize used in Italy is imported from Hungary and America, that therefore it would be impossible to find it perfectly sound, and that the withdrawal of the percentage of unsoundness would inevitably kill the trade in maize.

To show that with regard to the seizure of unsound maize the law is practically non-enforced, I need but quote a few of the facts mentioned at the last Pellagra Congress held at Udine, September 23 to 25, 1909.

Commendatore Cerutti, President of the Pellagra Commission of the Province of Venice, said: "At the meeting of the Commission, held in Padua, June 14, 1905, it was proposed:—

"(*a*) To obtain by means of the King's Prefects a greater vigilance on the part of the mayors, health officers, municipal guards, and policemen with regard to the breaking of Articles 1, 2, and 3 of the law.

"This is of great importance, but far easier to say than to carry out. It is true that the law prohibits to sell or hold, with the object of selling or supplying damp, unripe, or not perfectly dried maize and its products. It is true that this merchandise must be seized, and may no longer serve as human food. It is true that the offender is liable to a fine not exceeding 2,000 lire. But what is the use of all this if there be no persons with expert knowledge on the matter especially detailed to inspect shops, houses, bakeries, mills, &c.?

"The Commission addressed itself to the prefects, begged the mayors to put up notices, offered rewards to all such as would give information that might lead to conviction, but all to no purpose: the results were entirely negative.

"A few convictions were obtained, but the offenders had only imposed very small fines, and then were let off under the law of pardon.

"The Commission addressed itself to the Government authorities in order that means might be found so as not to render perfectly useless the first articles of the law, which are infinitely more important than any of the other measures contained in it. But until now it has been quite impossible to obtain anything at all."

And further, he explained that it would be impos-

sible for the Medico Provinciale, with the inadequate means at his disposal, to exercise throughout the whole of his province that constant daily supervision that would be so necessary. That it would be unreasonable to expect the overworked district health officer to repeatedly visit every house in his district to see that the peasants were provided with good maize, and that they kept it dry. And that in small places the local authorities could not be asked to take certain measures that would expose them to the ill-feeling and hatred of friends, relatives, or persons belonging to the same administration.

He mentioned the Commune of Cavarzere, a highly affected district which has over sixty mills along the River Adige. Asked to exercise special watchfulness over the maize that is brought to these mills to be ground, and on the flour that is returned in exchange for the grain, the mayor answered that it would not be possible to find anyone who would be willing to undertake so odious a task!

Professor Rezzara said: "But who has ever taken the trouble to observe or enforce the law?

"Our colleagues, Professor Stefano Balp, Chief Medical Officer of the Province, and Professor Pio Benassi, Director of the Unione Agricola Bergamasca, have pointed out to our Commission the very grave dangers arising from the enormous importation of foreign maize into Italy. A large proportion of this grain is ground in the large mills of Bergamo. And, indeed, the mills of the district of Bergamo alone can grind on an average 150 cwt. of maize in a day.

"And it is well to know that this enormous quantity of maize arrives by sea at the ports of Genova and Venice, but up to the present no precaution has been taken, or hardly any, notwithstanding the repeated appeals made to Government by our Commission."

Dr. Alpago-Novello, President of the Pellagra Commission of the Province of Belluno, stated that every

means of supervision hitherto attempted had failed signally. The offer of rewards for the denunciation of damaged maize which, it was believed, would certainly prove successful, had also failed, notwithstanding that comparatively large sums (100 and 150 lire) had been offered for each conviction. In his province, in five years, only three convictions had been secured.

Seeing that nothing could be obtained by appealing to Government, the Pellagra Commission of the Province of Venice took the bull by the horns and appointed, on December 13, 1907, a special pellagrological inspector. Two years later (1909) the Pellagra Commission of the Province of Padua also appointed a pellagrological inspector; and Professor Stefani stated that at the very start, in one of the larger towns inspected, this official found all the maize so greatly damaged that he was obliged to seize it from every corn merchant in the place.

But of the forty-four Italian provinces affected by pellagra, so far, only two (Venice and Padua) have a pellagrological inspector. The others as yet are without; however, in one of them, the Province of Bergamo, the provincial veterinary surgeon, since 1907, in addition to his many duties, has been entrusted with the inspection of maize.

At the Udine Congress (1909), where the question of maize inspection was fully discussed, it was unanimously resolved that each province affected by the disease should endeavour to appoint a special sanitary inspector for the proper enforcement of the first article of the law of July 21, 1902, concerning the abolition of unsound maize.

But even though it were possible for every province to appoint a pellagrological inspector, and all the inspectors were as upright, zealous, fearless, and indefatigable as the inspector of Bergamo, yet a great deal of unsound maize would inevitably escape detection. Amongst the many reasons, I might mention the

fact that a very considerable proportion of the maize eaten by agricultural labourers—the very people who suffer from the disease—never comes into the market, but is given direct by the owners to their men in part payment for their services.

But this is not all. There are many other facts which prove the inadequateness of any measure that can be taken to prevent the alimentary use of damaged maize. Thus, for instance, as pointed out by Ferrati, Marzocchi, Antonini, Mariani, and others, maize may be entirely spoilt and yet apparently sound and saleable. Or the grain may be quite sound, but after being ground the flour may sooner or later become tainted, especially if kept in a damp place. Or, again, the flour may be good and dry, but a few hours after being made into polenta it may become mouldy. At the Udine Congress (1909), Dr. Bonservizi, member of the Pellagra Commission of Mantua, stated that in the Provinces of Mantua and Verona maize is rarely found to be damaged, but that, on the other hand, it is the spoilt flour and mouldy polenta that there give rise to pellagra. Already at the Milan Congress (1907) he had pointed out that the peasants keep their polenta over night and eat it the day after it is made when already it may be decidedly mouldy. He was pleased, therefore, to hear Professor Audenino state that polenta can go bad in from two to three hours.

Finally, I must state that even when the health officer succeeds in confiscating some deteriorated maize, it not infrequently happens that either the municipal or the judicial authorities nullify his action. One district health officer told me that he had given up seizing maize long ago, because whenever he did so, the municipal secretary returned it to the owner. His action in the matter was, therefore, of no use to the public, but gave rise to enmities and rendered him unpopular.

Dr. Conti, in his report of the locanda sanitaria of Pellegrino Parmense, published in 1903, states that a large quantity of unsound maize which he had

seized was subsequently returned by the judicial authority and replaced on the market.

It is evident, therefore, that it would be unreasonable to believe that the elimination of damaged maize as an article of human food, ordered by the law of 1902, has been the cause of, or has in any appreciable way contributed to, the considerable decline of pellagra in Italy within recent years, as indicated by the official statistics, because, so far as maize inspection is concerned, the law was not acted upon until 1907 and then only in very few places, and to a very inconsiderable extent even there. On the other hand, since 1902, maize culture has been greatly extended throughout the peninsula and the importation of maize from abroad has very much increased. Besides, owing to the tolerance of 5 per cent. damage consented by Government, the millers have made it a practice of contaminating all good maize to that extent at least, in order to put to a profitable use their badly damaged grain. Under the circumstances it is obvious that it would be exceedingly difficult to find anywhere maize or its products without a large percentage of mould spores ready to develop as soon as placed in favourable conditions, whether at the mill, the granary, the village shop, or the peasant's house.

Exchange of Damaged Maize for Good Maize.

This measure, proposed in 1902 by Dr. Ceresoli, one of the most enthusiastic of Italian zeists, has been almost entirely restricted to the district of Bagnolo Mella in the Province of Brescia, and there even to a very limited extent.

Drying Apparatus.

The use of special apparatus for the purpose of drying maize to obviate its spoiling is no new measure in the fight against pellagra. On March 23, 1884, a royal decree was issued with the object of promoting the construction and adoption of drying plants,

by offering participation in the necessary expenses to the amount of half the total cost to be paid by the Minister of Agriculture to any municipality, agricultural society, charity organization association or other public body desirous of acquiring such apparatus. In 1895 there were already ninety-five drying plants in the Province of Brescia.

The law of 1902 gives the prefects of affected provinces the right to enforce the construction of one or more drying plants wherever necessary.

Several districts are now provided with drying apparatus of one or other type, but as a rule they are seldom used by the peasants, who, apart from inconveniences of various kinds (necessity of transporting either the grain or the apparatus for long distances, difficulty of obtaining the apparatus when required, all needing it at the same time, &c.), maintain that they damage the grain, depriving it of a certain amount of nutritive value, imparting to it an unpleasant taste, and impairing its power of germination. Besides, even after being dried, the grain soon deteriorates unless suitably stored in proper granaries, and, indeed, the grain dried in the apparatus at a high temperature is said to be more apt to become mouldy than that dried in the sun.

Rural Bakehouses.

The construction of rural co-operative bakeries for the making of good, cheap bread of wheat or maize is also an old measure. These bakeries were known as "Anelli bakeries," after the priest, Rinaldo Anelli, of Bernato Ticino, who warmly advocated their usefulness. About 1881 a number of these were constructed in the Provinces of Milan and Como, but they were not patronized and had to be closed.

The above-mentioned decree of 1884 offers the participation on the part of Government of half payment for the construction of rural bakeries. The law of 1902 makes no provision for such bakeries, but in

the instructions for the application of the law they are mentioned, together with the locande sanitarie, as obligatory. However, like the drying plants, so the rural bakeries have not proved at any time popular with the peasants, and therefore their usefulness, if any, has been extremely limited.

Abolition of Late Varieties of Maize.

The second Pellagra Congress that was held in Bologna in 1902 proposed that the Government should prohibit the cultivation of certain varieties of Indian corn, such as the "forty-day" and "fifty-day" corn, in all such places where, owing to local climatic conditions, these varieties do not ripen and dry sufficiently. But the rules for the application of the law of 1902 merely suggest the desirability of substituting other cereals or crops for those of the undesirable varieties of maize, and that only in districts affected by the disease.

Speaking of these rules at the third Pellagra Congress (Milan, 1906) Perissutti said: "These are rose-water rules which cannot certainly attain their object, because the district authorities have neither the moral influence nor the executive power necessary for the purpose. Moreover, they are illogical since in all probability they would only apply to districts in mountainous regions entirely free from pellagra, where maize does not ripen.

Notification of Cases.

The law of 1902 imposes the compulsory notification of all cases of pellagra even in its earliest stages, and this is certainly a most important measure aiming not only at a knowledge of the distribution and prevalence of the endemic, but also at the proper application of preventive and curative measures. However, the compulsory notification of pellagra is fraught with such numerous and serious difficulties that the results so far obtained are extremely unsatisfactory. One of the main difficulties is the diagnosis of the disease.

It should not be, because few diseases present such marked, peculiar, and unmistakable characteristics as pellagra, but none the less it is a true fact, and I have witnessed it repeatedly during my trip through the pellagra districts of North and Central Italy. In some places the diagnosis is somewhat obscured by frequent complication with other prevalent diseases, such as ankylostomiasis, for instance, but to my mind the greatest cause of uncertainty and confusion is the wrong etiological conception which, ascribing to the eating of maize the symptomatology of the disease, belittles its characteristic features to bring it in line with the appearances of malnutrition, indigestion, debility, and the various forms of food poisoning. The country doctor has been taught that pellagra is by no means a well-defined morbid entity, but an ever-changing assemblage of symptoms due to the lack of nourishment, indigestibility, and toxic properties of a diet composed almost exclusively of maize more or less damaged by various kinds of fungi and bacteria; that the characteristic skin eruption is often wanting and that alcohol may give rise to an exactly similar dermatitis. Thus misled, he not infrequently overlooks the real disease to take for it the most unlikely conditions. Thus everywhere I have found the early cases, especially in young children and infants, entirely overlooked, and cases of ankylostomiasis, ichthyosis, and vitiligo, looked upon as typical pellagra cases.

But apart from the ability of the physician and the views he may have with regard to the etiology and symptomatology of pellagra, there are many other circumstances that may considerably affect the notification of cases.

The health officer in charge of a large district cannot be expected to examine each spring the entire population of his division, especially if at that time he is dealing with an epidemic of enteric fever or some other disease; all he can do is to notify such cases as

seek his advice, or that he may casually meet on his rounds. But if he has time and is young, active, and enthusiastic, he may go to the trouble of a regular investigation, as, indeed, Dr. Sediari has done for the district of Trestina in a most praiseworthy manner.

In early cases the skin lesion is the only sign on which it is possible to make a correct diagnosis of the disease, but unless it be seen at the proper time it may be easily overlooked ; and, indeed, in many cases, especially in young children, the erythema may be very slight, of short duration and soon obliterated. In this stage the disease is not likely to attract attention, and will almost invariably escape unless specially looked for. The patients themselves look upon it as a mere sunburn, and in fact they call it " scottatura di sole," and give it no importance whatever, ascribing the accompanying symptoms to fatigue, indigestion, or biliousness.

Moreover, patients at a far more advanced stage, and presenting well-marked symptoms, are likely to escape detection on account of a sense of false shame which induces them to avoid the physician and forego certain advantages, such as free salt and free meals, to which their condition would entitle them. The disease is looked upon as degrading in many parts of Italy, and especially young women do all they possibly can to hide it for fear it should endanger their prospects of matrimony.

On the other hand, there are numbers of lazy, good-for-nothing people who, in order to obtain the advantages granted to pellagrins, endeavour to simulate the disease, and these have not only learnt to recite the symptoms usually regarded as distinctive of the disease—viz., debility, giddiness, insomnia, pyrosis, diarrhœa, salivation, &c.—but they will even mimic the confused mental condition and unsteady gait of the patient, and produce a spurious dermatitis or " bricklayer's itch " on the back of their hands by means of the application of lime.

Finally, I must mention another grave cause of error, and that is the deliberate increase or reduction of notifications in order to suit the special requirements of the local authorities. By the law of 1902 all districts declared to be affected are bound to provide free meals for their pellagrins, and drying apparatus, storage rooms, and rural bakehouses for the proper drying, preserving, and cooking of maize. One-half of the expenses necessary to fulfil these requirements must be paid by the local municipality, the other half is provided by the Provincial Board. Certain communes, finding themselves in difficult financial conditions, would be completely ruined by any heavy expense incurred for the feeding of numerous pellagrins; it is not surprising, therefore, that they should endeavour to avoid such expenses as far as possible, especially if convinced of the very dubious results of the locanda sanitaria, and of the inefficiency of the maize-killing measures adopted to fight the disease. Other communes being prosperous are only too willing to secure the monetary participation of the province in the upkeep of their charitable institutions. It is only too obvious that the local sanitarian, who is in the service and pay of the district authorities, must perforce concur in the views and interests of those from whom he depends. If a reduction be needed, he can very easily eliminate from his list all such patients as do not present very evident and certain signs of the malady, as well as those who, on account of complicating diseases, may be classified in a different way, besides he will not be over scrupulous in eliminating all those who, being more or less prosperous, can provide for themselves. If, on the other hand, an increase be required, he will have no difficulty in extending the present elastic diagnostic views in order to include numbers of miserable creatures debilitated by poverty, bad food, and ill-health, especially if they have been feeding almost exclusively on maize, as most of them do, or if they

can claim descent from parental pellagrins. And why not, so long as the disease is ascribed to the eating of maize, and is believed to be transmissible by heredity and atavism ?

Amongst the most flagrant cases of misrepresentation I came across is that of Clusone, a mountain district in the Province of Bergamo, the health officer of which had notified eighty-three cases. When I visited this district, together with Drs. Siler and Baldini, we could only be shown one single case of many years' standing. The others, the doctor explained, were not cases that would satisfy anyone making a special scientific study of pellagra, they were exceedingly doubtful, and had been notified for the purpose of keeping up the locanda sanitaria, it being the express wish of the authorities that a course of suitable food be given to those most liable to contract the disease. The local sanitarian was an exceedingly pleasant, intelligent, and well-read man, and we soon grasped his difficult position. He told us that at one time he used to see many cases of pellagra, the peasants of his district used to raise cattle and sheep, and frequently descended into the subjacent valleys with their herds and flocks, where they contracted the disease. Within recent years they had given up their former pursuits, and the majority of them migrated to distant parts of the world for periods of many years. He found ankylostomiasis in those who returned from Brazil, and saw even blackwater fever in those who had visited the West Coast of Africa, but pellagra had disappeared, and he had given up reading Lombroso to take up Manson's classical textbook of tropical diseases, of which he had an Italian translation.

With regard to what I have said it may be well to quote a passage from the Report of the Pellagra Commission of the Province of Venice, published in 1908. It reads as follows : "No one who knows the conditions of environment in which are placed many

of our district sanitarians will ever judge with severity the apparent complicity of these physicians ; some of them, and it is our duty to declare it, have expressed their great satisfaction for the control exercised by the delegates of the provincial commission, and asked for the greatest severity to be used in order that they might free themselves from the shameful pressures to which they are subjected, without exposing themselves to unpleasant consequences."

For my part I must say that, in consequence of a very pleasant experience amongst hundreds of them, I have come away with the highest possible opinion of the energy, skill, integrity, and devotion of the Italian district physician.

The Locanda Sanitaria.

The law of 1902 imposes that in all affected districts poor pellagrins shall be given free meals for periods of not less than forty days twice every year. To this measure, which is looked upon as a means both of cure and prevention, is chiefly ascribed the great decline of the disease in recent years. And, indeed, if such a decline has really taken place, and if it can be ascribed to any of the measures adopted in the fight against pellagra, this must be the measure, for the reason that it is the only one that has been carried out to any reasonable extent.

The reports of the various commissions as a rule, speak very favourably of the results obtained by the alimentary treatment, and present figures, neatly tabulated, which appear to be irrefutable. Unfortunately, the real facts are very different. In the first place the treatment is in no way beneficial to advanced pellagrins, especially if elderly. This fact is so fully recognized that such cases are entirely excluded from the locanda. Young people in the early stages of the disease and very mild cases are admitted, and these do certainly improve and gain weight during the period of treatment. These cases

are invariably reported as cured at the end of the period of treatment. But this is a mistake, and is known to be a mistake. Improvement would take place even without any special treatment; it is one of the characteristics of the disease for its symptoms to abate in summer and almost entirely disappear in winter, to return with renewed power in the following spring. And it is a well-known fact that the pellagrin commensals of the locanda sanitaria return year after year until refused admission, or prevented by the aggravation of their infirmity. That the increase in weight and a certain amount of improvement is really due to the food received at the locanda sanitaria, I do not doubt in the least, all I wish to do is to place facts in their true light.

A still more serious fact to be brought against the beneficial results ascribed to the locanda sanitaria, in so far as pellagra is concerned, is that the majority of those admitted are not pellagrins. This fact was repeatedly observed by Dr. Siler, Dr. Lavinder and myself throughout Italy. In some of the locande sanitarie not one-third of the inmates could be looked upon as true pellagrins, and, as a rule, not one showed active manifestations of the disease. This fact impressed us very forcibly, because we had relied on the locande sanitarie for the collecting of valuable information and material, and our disappointment was great when we found them to be mere depôts of mendicity.

The explanations already given with regard to errors in the number of cases notified may account to a certain extent for the presence of numerous non-pellagrins at the locande sanitarie, and, indeed, many of the commensals are not entered on the roll as pellagrins, but only as " minacciati " a comfortable word literally meaning menaced or predisposed, but, like many more of its kind, used to cover ignorance as well as a multitude of mistakes, difficulties, and frauds.

What surprised me most was that although I could find no good cases of pellagra at the locanda

sanitaria, a house-to-house visitation throughout the district would usually reveal numerous typical cases to whom the treatment was not extended.

Irregularities of the kind have already been pointed out by others. Thus at the third Pellagra Congress of 1906, Drs. Randi and Deganello stated that the locande sanitarie "are much too often frequented by non-pellagrin commensals."

All the pellagrins we discovered in our excursions were not on the lists of notified cases, but a number of them were, and yet these unfortunate creatures had not been granted admission to the locanda sanitaria. The reason is that the meals distributed are not provided in proportion to the number of pellagrins present in each district, but in reason of the more or less restricted sum the local authorities can dispose of. Thus, even though all those admitted were true pellagrins, the treatment would reach only a very small proportion of those entitled to it by the law of 1902.

One great objection to the locanda sanitaria is that of its distance from the endemic stations of the disease. It is invariably situated in the principal inhabited centre of the district where, as a rule, there are no pellagrins and therefore it is of no use to the real pellagrins who, living at a great distance, are unable to reach it. Some of these poor creatures have at times dragged themselves long distances day after day to eat the pellagrifuge soup, but the fatigue has invariably outweighed the benefit derived from the food. In recent years, it has been a rule not to admit any one living outside of a reasonable walking radius. This again is a limitation which necessarily excludes not only a great number of pellagrins but, at the same time, the most desirable cases.

Although enthusiastically extolled at one time the locanda sanitaria is now gradually loosing favour. Its uselessness in either curing or preventing the disease, its failure to reach the true pellagrin, have been fully realized, and, indeed, at the last Pellagra

Congress, Professor Antonini stated that the locanda sanitaria could be considered beneficial only as a means of individual treatment and not as a general measure of prevention and prophylaxis. He said "the locanda sanitaria has the great defect of being limited in time, it cannot dry up the perennial sources of the pellagrogenous flood, and every year the renewed host of pellagrins will knock again at the door of the locanda, because every year the maize poison, in the form of food, finds its way of entry into those who return from the locanda as into the rest of the agricultural population," and he proposed to substitute for the old locanda sanitaria the distribution of free food to pellagrins at their very house by means of ambulatory kitchens.

The facts brought forward fully justify, I think, a very serious doubt as to the part ascribed by some to the locanda sanitaria in bringing about the recent decline of pellagra. The locanda sanitaria[1] is an old institution already widely adopted before 1902. Of the affected communes only a comparatively small number are provided with a locanda sanitaria; the number of persons admitted represent but an infinitesimal proportion of the pellagrous population of the district; of those admitted, a large proportion are not pellagrins; the results of the treatment in true pellagrins have been almost entirely negative.

The Pellagrosario.

The first pellagrosario was that of the Duchy of Milan, opened at Legnano in 1784, by order of Joseph II. of Austria. It lasted only four years, but will remain ever famous in the annals of medicine on account of the masterly observations there made by Gaetano Strambio, the physician in charge.

[1] The Province of Bergamo was the first to institute the locanda sanitaria in 1884. Then followed Padua in 1892, Brescia in 1894, Venetia, Ferrara, and Umbria in 1896, Udine and Vicenza in 1897. In 1901 the Province of Bergamo had no less than 42 locande sanitarie.

The pellagrosario of the present day is nothing more than a locanda sanitaria with bed accommodation added. There are only a few in the whole of Italy. Those of Inzago, Città di Castello, and Mogliano Veneto are the most important. At Inzago the inmates are chiefly children; they are taught to read and write during the period of their stay which is of about three months each year. At Mogliano Veneto the inmates are chiefly adults and they are expected to do a certain amount of agricultural work. I have visited the pellagrosari of Inzago and Città di Castello; in the first there were no pellagrins. Dr. Fritz, who has been in charge since the foundation of the institution, told me that in recent years the disease has almost entirely disappeared and that the children under his care are, for the most part, the progeny of old pellagrins. At Città di Castello the inmates of the pellagrosario were for the most part of the type met with at the locanda sanitaria; two, however, were very interesting: one was a boy about 16, with marked erythema in the acute stage, and the other an infant 7 months old, presenting well-marked patches of erythema on hands and face.

Salt.

Of the various measures proposed by the law of 1902, the most extraordinary is the one concerning the dispensation of a certain amount of salt to all poor pellagrins and their families. So far as I know, no one has ever shown that salt is either of preventive or curative value in pellagra, but some of the older writers, especially in view of the fact that salt is a Government monopoly in Italy, have ascribed the disease to the eating of polenta without salt. It is probably on account of this peculiar and unfounded etiological view that the distribution of free salt has been adopted as a prophylactic measure against the disease.

The free salt is dispensed either monthly, fortnightly,

or weekly, to the total yearly amount of 8 kilogrammes for each adult and 5 kilogrammes for each person below 15 years of age. Orders for the application of the articles of the law of 1902, relative to the free distribution of salt, were issued on January 27, 1904.

The application of this measure is as unsatisfactory as that relative to the dispensation of free meals. As soon as it became known in the affected districts that those suffering from the disease would be granted free salt, numerous applications were made by pellagrins as well as by non-pellagrins. The health officers were somewhat easy in granting the advantage, and the communal authorities saw no objection to a charitable measure which cost them nothing. But the granting of free salt to many people who were not entitled to it, and the practice followed by many recipients of exchanging it for spirits or tobacco, brought about a restriction of the concession on the part of the Ministry of Finance.

I have come across one or two non-pellagrin, town-inhabiting families who were benefiting by this measure, but, on the other hand, at Morra, Paradiso, and other places, true and often severely affected pellagrins, taking me for some kind of salt-distribution inspector, have complained to me either because the article had not been granted to them or because it had been withdrawn. At Trestina, among those who had not been granted the benefit of the free salt was a ragged, barefooted peasant, aged 64, wearing a large poultice of cornflour round his forehead and two medals on his breast. His name was Severino Montani, he had rushed Porta Pia under the papal fire, and saved lives in the flood of Rome in 1870. He had been a pellagrin for some years, and was now quite unable to work. His head was very painful and that is why he had had it poulticed. He said he could not lift up his head without falling —"the world around him became at once quite dark." And this man, now aged and disabled, was

grudged a pinch of salt after he had placed his very life at the country's service.

If I understood rightly, the revocation of a number of salt grants was effected by the fiscal agents without the consent of the district health officer.

From all I have said I think it is quite evident that the law of 1902 can have caused no appreciable change in the prevalence of pellagra. This law has not introduced any new measure; all those which it has adopted were already in use and had been in use for several years, under the supervision of the very same local commissions now continuing them on behalf of the Government. The law did not come into full force until 1907, and, even after that date, its application has been very limited. The inspection of maize is no easier to-day than it was in the past, and has yielded no better results. Drying apparatus and rural bakeries have not proved more popular than in the past, the change of bad for good corn has remained in the field of praiseworthy intentions, the locande sanitarie have not given any better results than in the years preceding the law, and are now losing favour, the pellagrosari are few in number, their action has been at all times extremely limited, and, so far as concerns the cure and prevention of pellagra, very doubtful. The use of salt has not proved more effective in the prevention of pellagra than in the capturing of birds.

The measures adopted and enforced by the law of 1902 are, every one of them, founded on the belief that unsound maize is the true and only cause of pellagra. It was argued that this being so, the elimination of unsound maize from the market and the dispensation of free meals and salt to all pellagrins must necessarily wipe out the "humiliating disease."

But, as I have endeavoured to show, the maize theory is wrong, and, therefore, the measures based upon it, even if thoroughly carried out, would have failed to stamp out the disease

In Italy the theory which ascribes pellagra to damaged maize is an official theory. It is the theory of the statistician who has never seen a case of pellagra, of the laboratory investigator who has studied only damaged maize, of the physician of the insane asylum and of the pathologist who have seldom if ever visited the haunts of the disease. I have not found it to be the theory of the district physician. It is true that the district physician has a vague idea that maize must play some part in the causation of the disease. He cannot help being impressed by a theory that is taught in every school, published in every book, and asserted by men who use microscopes and experiment on rats and guinea-pigs, but against all this stands his own experience of facts read straight away from the great book of Nature. He knows that the disease is not equally distributed throughout his district; if you ask him he will tell you at once, without the least hesitation, the names of the places which, year after year, give the contingent of cases. He knows perfectly well that this peculiar distribution of the disease cannot be accounted for by maize, which is eaten in all places alike, nor by bad maize, which shows neither a special nor a constantly identical distribution. He knows of many poor people who have always eaten the very worse maize, and yet have never presented any signs of pellagra, and he knows of cases of the disease in persons of means who have seldom or never eaten maize. Yet, notwithstanding the experience of many years, he has no definite idea with regard to the causation of pellagra. He is inclined to think that poverty, uncleanliness, starvation, bad maize, lack of wine, may, somehow, bring about the disease, but in his opinion these conditions are predisposing causes, and leave still open the question of the true causative agent. Unprepared to carry out scientific investigations, overworked by the duties of his post, he has neither time nor inclination to solve the mystery, and

year after year the outbreak of pellagra overtakes him as helpless as ever to cope with it.

"Why do you believe in the maize theory?" I asked a physician, who had been telling me of the unequal distribution of the disease in his district, and of two pellagrins who had never eaten maize. "I do not believe in it," he answered, "but everybody does, and there is nothing I can suggest to replace it."

The maize theory is now spoken of in Italy as the "Lombrosian theory," and the name is suitable; not that Lombroso suggested the theory, but because he and his school imposed it with a dogmatism and intolerance inconsistent with the spirit of modern science.

The imposition of official views with regard to pellagra is no new episode in the annals of medicine. Not long ago it was not permissible to young army surgeons to suggest the existence of enteric fever in India, because superior officers held that it was unknown in the Gangetic peninsula.

It is no doubt owing chiefly to the "Lombrosian theory" that for over thirty-six years no real progress has been made in the elucidation of pellagra. Instead of forwarding the investigation of the disease, the reasserted theory brought all attention to bear on the study of deteriorated maize.

Of all those who have endeavoured to establish the maize theory of pellagra on true scientific data, no one has worked more ably and conscientiously than Professor Gosio, chief of the Public Health laboratories in Rome, and I can do no better than quote some of the conclusions in his paper on "The Etiological Problem of Pellagra," published in 1906. He says:—

"Now we must judge whether all these studies have only a pure scientific character, or whether they also have that practical significance which is so important to us, the elucidation of pellagra.

"It is certain that anyone believing in a true relationship of cause and effect between toxic moulds and pellagra cannot help *virtually* thinking of a

pellagra without maize. In publishing the results of our earliest researches, we expressed such a *virtual* probability ourselves, *always, however, subordinating it to the confirmation that such intoxications do really constitute pellagra.*

"There is no doubt that the various toxic hyphomycetes isolated from maize have the potentiality of producing a form of poisoning that has several points of resemblance with pellagra, *but, in truth, whether this be really pellagra, or all the pellagra observed in practice, and whether the symptoms undoubtedly specific which can be produced in animals by means of hyphomycetic poisons represent the pellagra of man, are matters which still require demonstration.*

"The lead to researches truly useful and fruitful must proceed from the careful examination of various types of pellagra, and from the epidemiological study of the disease which so far has been considerably neglected and almost entirely supplanted by laboratory investigation."

During my investigations in Italy, I have devoted considerable time and attention to the examination of maize, and I found that the distribution of deteriorated maize does not in any way coincide with the distribution of pellagra.

Miss Lorrain Smith, assistant in the Botanical Department of the British Museum, who has kindly undertaken to study the hyphomycetic flora of the maize collected by me, states that in samples of badly deteriorated grain from healthy localities, besides *Penicillium glaucum*, Link., which is the chief cause of deterioration, she has found species of *Aspergillus*, *Tricothecium*, and *Alternaria*.

At first, I thought that some kind of indirect connection might be found to exist between maize and pellagra. Some sort of connection similar to that which exists between the swamp and malaria. Therefore I was greatly interested to read in King's notes on "Blood-sucking Insects other than Mos-

quitoes," published in the third report of the Wellcome Research Laboratories, Khartoum, that the natives of the Dongola province connect the presence of sand-flies with the raising of a grain crop. But, so far, I have been unable to trace any connection whatsoever between maize and pellagra.

One day I asked a pellagrin peasant of Bergamo what he thought of the maize theory. He answered, " Sir, it is not maize, but the want of maize that causes pellagra."

The Simulium Theory.

As already stated, before leaving London to carry out the present investigation, I had come to the conclusion from previous observations and reading that pellagra had nothing to do with maize, but that it probably was a parasitic, insect-borne disease, and that the necessary carrier might prove to be a blood-sucking fly of the genus *Simulium*.

My reasons for this belief were the following :—

(1) *Pellagra is a parasitic disease* because :—

(*a*) The characteristic eruption and other symptoms of the disease may recur each spring for a number of years, notwithstanding the removal of the patient from the endemic districts and the strict elimination of maize from his diet. This peculiar periodicity of symptoms can be explained only by the agency of a parasitic organism presenting definite alternating periods of latency and activity. Analagous periodicities are met with in other parasitic diseases—as, for example, in tertian fever, in which the periods of activity of the parasite (*Plasmodium vivax*) recur each summer in correlation with the activity period of its anophelic definitive host. No toxic substance could account for it.

(*b*) It presents peculiarities of distribution

and seasonal incidence as in all parasitic diseases.

(*c*) Its symptoms, course, duration, morbid lesions are analogous to those of other parasitic diseases.

(2) *It is an insect-borne disease* because :—

(*a*) It is not directly contagious.

(*b*) Neither food nor drinking water can account for its peculiar epidemiology.

(*c*) It is limited to certain rural districts only, towns and villages almost invariably escaping.

(*d*) It presents a definite and peculiar seasonal incidence—viz., spring and autumn.

(*e*) It is practically restricted to only one class of people—viz., the field labourer, owing to greater exposure to infection.

(3) *It is conveyed by a Simulium*, because :—

(*a*) Simulium, so far as we know, appears to affect the same topographical conditions as pellagra.

(*b*) In its imago stage it seems to present the same seasonal incidence.

(*c*) It is found only in rural districts, and, as a rule, does not enter towns, villages, or houses.

(*d*) It explains most admirably the peculiar limitation of the disease to agricultural labourers, a limitation which nothing else can explain in a satisfactory manner.

(*e*) It has a wide geographical distribution which seems to cover that of pellagra, although certainly exceeding it, in the same way that the distributional area of the Anophelinæ exceeds that of malaria, and the range of *Stegomyia calopus* that of yellow fever.

(*f*) It is known to cause severe epizootics in Europe and America.

(*g*) Other similarly minute blood-sucking diptera such as *Phlebotomus papatassi* and *Dilophus*

febrilis are strongly suspected of being propagators of human diseases.

The Disease.

In order to be able to grasp the true nature of pellagra, it is necessary, in the first place, to have a perfectly clear picture of its clinical and epidemiological features. In Italy I was somewhat surprised to find physicians who, notwithstanding long years of practice in the affected districts, confounded pellagra with ankylostomiasis, chronic dysentery, syphilis, vitiligo, and other very different diseases. Several of them told me that they diagnosed pellagra by the general appearance of the patient, the peculiar gait, the debility and giddiness, the anæmic condition, a furrowed and papillated tongue, epigastric pain or uneasiness, pyrosis, and diarrhœa, and not by the erythema which, in their experience, might be either frequently absent or easily confounded with a strikingly similar eruption due to ethyl alcohol and, accordingly, called "ethylic erythema." In view of this opinion, expressed not only by country doctors, but by prominent university teachers, I determined to pay special attention to the cutaneous manifestations of the disease. Very soon I found that those who held the erythema to be frequently missing, had either overlooked it or confounded other diseases with pellagra, and that the so-called "ethylic erythema" is nothing more nor less than the pellagra dermatitis in alcoholics.

Diagnostic Value of the Eruption.

My own experience, founded on the examination of very numerous cases, leads me to consider the pellagrous eruption as the earliest, most distinctive and essential manifestation of the disease. Its features are characteristic and striking. It occurs in spring or early summer, rarely also in autumn, and is limited, almost exclusively, to the agricultural population of

certain well-defined endemic areas. It appears suddenly under the action of the sun's rays and affects those parts of the body which are ordinarily bare and exposed to the sun, such as the back of the hands, the face, the neck, and, when bare, the extensor surfaces of the feet and legs, the forearms, the upper part of the chest and back. It appears in the form of more or less symmetrical patches of a bright red, or deep red, colour, with sharply defined margin. The affected parts are more or less swollen and the patient experiences a painful sensation of burning or tingling, which becomes particularly acute under exposure to the action of the solar rays. The rash stands out for some days and is followed by marked and persisting desquamation, leaving the skin pigmented, thinned and parchment-like.

In cases of a mild type, especially in young children, the pellagrous rash may very easily escape observation being not infrequently scarcely perceptible, and soon, disappearing without leaving any trace. In such cases it may be mistaken for an ordinary sunburn, as Strambio pointed out over a century ago. I have no reason to doubt that pellagra may exceptionally occur without any cutaneous manifestation and that we may speak of a "*pellagra sine pellagra*" as we do of "*morbilli sine morbillis*," of "*scarlatina sine scarlatina*," and even of "*variolæ sine variolis*." But I am inclined to believe that the majority of cases of pellagra without eruption are to be accounted for by evanescent undiscovered rashes, and this is all the more probable when the actual presence of desquamation obviously suggests an antecedent cutaneous inflammation.

In children, I have frequently noticed the extreme mildness, brief duration, and complete disappearance of the cutaneous marks, and I believe this to be one of the reasons why so many authors have wrongly stated that pellagra is a rare disease in young children. Of the older authors, I might mention Odoardi (1776),

who says: "I have not seen it in either boys or girls younger than 6 or 8 years of age," and Soler (1791), who says: "Children below the age of 12 years are exempt from this disease." Of modern authors I will mention Sandwith (1905), who says: "I have not seen cases under the age of 5 years, and it is quite rare under 10." Against these are others who have observed it frequently in children, thus Strambio (1794) says: "As to age, I had already published many histories of pellagrous children, not only under 12 years of age, but 6, 4, 2, and even in sucklings, therefore Soler had no right to say that those under 12 years are exempt; if he has not observed it, he should not state on that account that it cannot be"; and Warnock (1909) says: "Pellagra is very common in children in Egypt. I have seen scores of children from 10 to 15 dwarfed, cachetic, anæmic, and displaying splendid black pellagrous rashes, and usually insane."

Even when marked, the pellagrous eruption in young children soon disappears and seldom leaves any trace. I have had the opportunity of observing this fact several times. The first case was that of Umberto Pavinato, a child, aged 3, seen at Chiesanuova, near Padova. When first I saw this case on April 23, together with Dr. Siler and the local physician, Dr. Carrer, the rash on hands and face was very marked, the hands seemed to have been dipped into some purplish dye. The face presented a veritable mask extending from the roots of the hair to below the mouth. On the neck was the characteristic neckband described by Casal. The next day when I saw him again with Drs. Lavinder and Blue, the rash was slightly paler, the child was feverish and depressed. Three days later, I had the child photographed, but the eruption had faded considerably and the face had a peculiar wrinkled appearance, whilst the cuticle was desquamating in scurf-like scales. A few days later, it would have been impossible to make

a diagnosis. The child had contracted the disease two years previously in the Province of Rovigo, and had already twice before presented in spring the characteristic eruption.

A second case was that of an infant, aged 7 months, that I saw at the pellagrosario of Città di Castello on June 2, This infant presented an unmistakable pellagrous erythema on face, hands and feet. Dr. Fabbri, Director of the Pellagrosario, told me that the eruption was even more marked a few days before when the infant was admitted together with its mother, who was herself a pellagrin, having contracted the disease a year ago at Passano, where she had then moved from some healthy village in the Apennines. A few days later, when I paid my last visit to the Pellagrosario of Città di Castello, every trace of the eruption had disappeared.

A third case was that of Nunziata Bettachioli, a girl, aged 14, who lived at Promano, near Città di Castello. This girl presented a well-marked rash on face, hands, and forearms, and had been a pellagrin since early childhood, the characteristic eruption recurring invariably each spring. I took this patient over to London, hoping to be able to show at the London School of Tropical Medicine a typical pellagrous eruption, but, on arrival, there remained only a slight roughness of the affected parts, and, now, even that has completely disappeared.

Not only have I found the eruption to be the earliest and most conspicuous manifestation of pellagra, but in a large number of cases it is the only symptom by which any diagnosis can be made; therefore, I am unable to agree with Dr. Sandwith (1905), who says: "I hope to show that the disease should never be diagnosed by the eruption alone," but on the contrary, with Professor Merk (1909), I consider the cutaneous lesions of pellagra to be of the same importance as are the eruptions of variola, measles, and other exanthemata in the diagnosis of these diseases.

Ethylic Erythema.

In Italy, for many years, it has been held that the lack of wine might be an important predisposing cause of pellagra, and the use of this fermented beverage has been widely proposed and adopted as a means of cure and prevention. In recent years, however, alcoholism has increased to an alarming extent among the rural populations of Northern Italy, and we now find a complete reversion of opinion, and pellagra ascribed to the immoderate use of alcohol. Some authors justly recognize the superposition of alcoholism upon pellagra; others believe that alcohol itself may give rise to cutaneous lesions strikingly similar to those characteristic of pellagra. Even in insane asylums I found pellagrins diagnosed as alcoholics, especially when maize could not be considered a causative factor in the case, whilst the abuse of alcohol was indubitable. Some authors have gone so far as to actually describe diagnostic differences between the pellagrous eruption and the so-called ethylic erythema. Thus Majocchi states that the alcoholic erythema (pellagroid) shows no sharp margination; is more persistent, and slower in causing pigmentation. Breda adds that it is rare, limited to adult males, of slow evolution, non-symmetrical, that it presents no seasonal intermittency, and does not usually give rise to atrophy of the skin.

At the last Pellagra Congress (1909) Dr. Zanon, Director of the Insane Asylum of Treviso, stated that, in the spring of 1909, a sudden increase had been reported in the number and severity of pellagra cases in certain districts of the Province of Treviso. In the three previous years the disease had gradually and progressively diminished. Thus in 1906, 730 cases had been reported; in 1907, 593; in 1908, 364. But in the spring of 1909 no less than 676 had been notified. It looked, therefore, as if "all prophylactic victories were only apparent, fictitious!" However,

in consequence of a hasty investigation by means of questionary circulars to the district health officers, Dr. Zanon came to the conclusion that the alarm raised in the spring of 1909 was unfounded, "because in the majority of the notified pellagrins alcoholism played a not unimportant part."

This example, like many more which might be adduced, discloses a curious, unwitting tendency on the part of certain Italian pellagrologists to endeavour to hide or minimize the actual extent of pellagra; and is probably suggested by an unwillingness to recognize the failure of the measures adopted to prevent a disease which, strange to say, has long been regarded as a shame rather than a calamity.

Having never seen any erythema that might be confounded with that of pellagra in the alcoholics of other countries, and having ascertained the specific characteristics of the pellagrous eruption, as well as the necessary residence in a pellagra station at the time of onset, in all such persons as were indicated to me in Italy as subjects of ethylic erythema, I am unable to admit of its existence. Besides, the Italians themselves believe that their "ethylic erythema" may be due to the drinking of maize-derived alcohol, thus abolishing their own distinction.

Complication with other Infections.

An important cause of confusion in the diagnosis of pellagra is that of combination with other diseases.

In places where pellagra is frequently seen in association with either scurvy or ankylostomiasis, the added symptoms of these diseases are likely to be looked upon as pertaining to it, and when found alone may still be regarded by some as manifestations of a pellagra without eruption. And the mistake is all the more easy when the scorbutic or anæmic patient is in addition the subject of some cutaneous affection, such as ordinary sunburn, erythema multiforme, eczema, or vitiligo.

The possibility of confusion with scurvy, ankylostomiasis, and other diseases, is not in the least surprising when we consider the frequency of association of such diseases with pellagra, and the impossibility for the ordinary country doctor to make a proper discriminating diagnosis for lack of the necessary knowledge, experience, and apparatus.

Complication with Scurvy.

The co-existence of scurvy and pellagra is not uncommon in certain districts of Northern Italy, but, in days gone by, scurvy appears to have been more prevalent, and consequently its association with pellagra more frequent. Indeed, before being recognized as a distinct morbid entity, pellagra was confounded with scurvy.

Of the older writers on pellagra, Soler (1791) is one, for instance, who describes the scorbutic symptoms as indications of pellagra. He says: "Having reached this stage, the patients feel a pricking sensation in the gums; these become swollen, and bleed at the slightest touch. The teeth become black, decay, and fall out of their sockets; on the palate at times appear blebs; the raised cuticle is removed from its surface, and spreads the process throughout the interior of the mouth. Under such conditions the breath smells abominably."

Aldalli, mentioned by Solar, says: "This disease (pellagra) seems to be a scorbutic affection of a particular kind, I have always described it as such, and pointed out that it differs from the ordinary scurvy, which at times may also be seen in these localities (Sarone, a village at the feet of the Julian Alps) in other subjects."

Whilst a number of physicians confounded scurvy with pellagra, others, like Strambio, Videmar, and Fanzago, declared the two diseases to be quite distinct. Videmar recognizes that pellagra may

frequently co-exist with scurvy, but, he adds, "a scorbuto autem quantum distat!"

Fanzago (1792), in his famous parallels between pellagra and other diseases, says: "The error of confounding these two diseases one with the other is due to the confusion which is made between the secondary and accidental symptoms, and those which are primary and constant, an apparent analogy resulting thereby, thus, for instance, such symptoms as the corruption of gums and decay of teeth, inseparable from scurvy, have occasionally been observed in pellagra. In scurvy they are primary symptoms, in pellagra only accidental."

Notwithstanding the teachings of Strambio, Fanzago, and the generality of Milanese physicians, those of Venetia continued to confuse scurvy with pellagra.

Marzari (1810) points out that: "In pellagra the parts of the mouth most affected, and at times the only ones, are the soft palate and the fauces, and not the gums as in putrid scurvy." He says this differentiation is based, not only on the writings of numerous authors, but on his personal observations of "northern scurvy" in the Department of Treviso, and he says Widemar is wrong in denying the existence of "putrid scurvy" in Italy, because, though rare, it is none the less present; and he mentions its presence also in the Valley of the River Serio, where Da-Ponte noticed it in 1803.

Both scurvy and pellagra occur in the beginning of spring, both are generally ascribed to insufficient or inappropriate food, both cause great debility and marked mental apathy, and one can easily imagine how the intermingling of pellagrous erythema and scorbutic ecchymoses in every possible degree may have occasionally induced the physician, with no other than strictly local experience, to confound the two diseases and diagnose the one by the symptoms of the other.

In the Province of Bergamo, where cases of scurvy

are even now occasionally seen, I noticed that several of the local physicians invariably examined the gums of their pellagrin patients. On the other hand, in the Province of Perugia, where scurvy appears to be unknown or very rare, no one ever thought of looking for swollen or bleeding gums.

Complication with Ankylostomiasis.

The great frequency of the association of pellagra with ankylostomiasis is well known. Dr. Sandwith (1905) has pointed it out for Egypt. He says: "So long ago as 1893, while preparing a paper on ankylostomiasis, I became aware that some of my peasant patients at Kasr-el-Ainy Hospital in Egypt were suffering from dermatitis, bald tongue, diarrhœa, pains in the back, alteration of the knee-jerk, insomnia, and melancholia, all symptoms which could not legitimately be attributed to the anæmia caused by the hookworm."

In Italy this association is just as common. Pisenti and Mandolesi (1901) have shown that this is the case in Umbria, and Fabbri (1902) has confirmed their researches.

Pisenti and Mandolesi say: "It is well known that one of the most prominent features in pellagrins is their grave anæmia. There is reduction in the number of erythrocytes, reduction in the hæmoglobin, reduction in the isotonic power . . . . now, in examining fæces submitted to us for the purpose of diagnosis, we were able to notice that fæces containing numerous ankylostoma eggs appertained to pellagrins, and that, as a rule, they belonged to pellagrins profoundly anæmic. This fact led us to devote our attention to the frequent concomitance of the two conditions: grave anæmia in pellagrins and presence of ankylostoma eggs in the fæces."

Then the authors examined the fæces of numerous pellagrins gathered in the pellagrosario of Città di Castello and found in all many ova of agchylostoma.

Besides, they were able to ascertain that the pellagrins presenting the gravest oligœmic forms were those who presented the greatest number of agchylostoma eggs in their fæces. In conclusion they state that their numerous observations authorize them to make the following suggestion: "Is it not possible that the anæmia of pellagrins, besides being sustained by the special conditions induced in the human organism by pellagra, may also frequently depend upon the presence of ankylostoma which might act as an associated cause, being alone capable, as is well known, to produce the picture of a grave anæmia?"

The observations carried out in Italy by Dr. Siler and myself on this point show quite conclusively that the "pellagrous anæmia" of Italian authors is undoubtedly a complication and usually a complication with agchylostoma.

Captain Siler examined the stools of over a hundred general patients in the hospital of Bergamo, and I subsequently examined the stools of a number of pellagrins and would-be pellagrins in various districts of Lombardy and Umbria, with the result that we found *Agchylostoma duodenale* to be very frequent in pellagrins and non-pellagrins of certain districts. Besides *Agchylostoma duodenale*, we found *Ascaris lumbricoides*, *Trichiuris trichiura*, *Oxyuris vermicularis*, *Cercomonas hominis*, *Entamœba coli*, and, once, in the fæces of a child, in Bergamo, the ova of *Hymenolepis nana*.

The wide distribution and great prevalence of ankylostomiasis in Italy among rural labourers has been pointed out by several authors. Indeed, it was in Italy that Dubini (1843) discovered in 1838 *Agchylostoma duodenale*, and it was in Italy that Grassi and Parona (1878) showed how its presence could be diagnosed in the living host by the finding of its ova in the fæces.

Since the discovery of *Necator americanus* by Stiles in 1902, several authors have recognized this parasite

in Italy, and its recent importation from America has been suggested especially by Messedaglia and Siccardi, who have found it in Italian emigrants returning from Brazil. Its constant reintroduction is an undoubted fact and one of considerable importance with regard to the wider diffusion of this species in Italy. It is quite possible, however, that its presence in Italy is of old date. The researches of Looss, Stephens, and Leiper have shown that *N. americanus* and other as yet undescribed species of Stile's new genus belong to the Old World from which they were probably imported into the Western Hemisphere at the time of the slave trade. Another intestinal parasite which is being constantly reintroduced by returning emigrants is *Strongyloides intestinalis*. Messedaglia (1907) points out that he very seldom found this parasite in the peasants of the Paduan territory, but frequently, together with *N. americanus*, in emigrants returning from Brazil. However, while Necator was not recognized in Italy until after it had been differentiated by Stiles, *S. intestinalis* was found and determined by Grassi as early as 1878

Besides anæmia, other symptoms, often ascribed to pellagra, are referable to the complicating ankylostomiasis. Such are œdema of face and ankles, ravenous or abnormal appetite, pain and tenderness in the epigastrium. On the other hand, many symptoms are common to both conditions, and thus the emaciation, bodily weakness, mental lassitude, anxious and stupid expression, parchment-like skin, loss of patellar reflex, denudation of tongue, insomnia, headache and dizziness of ankylostomiasis, especially when coupled with certain cutaneous affections, are likely to mislead the district physician into an erroneous diagnosis.

Other Complications.

Many other diseases may complicate pellagra and be confounded with it. In Spain and Italy, over a century ago, pellagra was mistaken for leprosy.

Corre (1887) points out that in Tropical America it is probably often confounded with pinta, and Bazin (1865) tells us that in France it has been confounded with common ringworm. A not infrequent and important cause of error is syphilis. Marie (1909), the eminent French psychiatrist, who has studied the subject in Egypt, says : " A certain number of insane paralytics coincide with pellagra and confirm the opinion of Baillarger, that the final paralytic phase of pellagra can represent an identical state clinically and pathologically with general paralysis of the insane. These cases do not invalidate at all the other form of general paralysis from which they are distinct, and which I have described as being in relation to syphilis. The two factors can, however, be combined, that is to say, one may observe among the Arabs general paralytics who are at once both syphilitic and pellagrous."

Importance of Associated Infections.

Associated infections and other debilitating conditions have a very marked influence in predisposing to the development of pellagra and in rendering its course more rapid and severe.

In quite a number of cases I found that the manifestations of pellagra had followed upon an attack of some antecedent disease such as enteric fever, malaria, dysentery, rheumatic fever, whooping-cough, cardiac disease, or some other debilitating affection. In women, pregnancy and parturition seem to be very common predisposing causes. In one patient traumatism appeared to have determined the outbreak of the disease. Many other diseases are similarly influenced by antecedent or concomitant maladies. It is well known that a latent tuberculosis may be suddenly awakened into activity by an attack of enteric fever or measles, that in children suffering from whooping-cough the rubeolar eruption is remarkable for its intensity, that pulmonary tuberculosis,

pneumonia, erysipelas, run a rapid course in diabetics, whose glucose-steeped tissues seem to attract every kind of pathogenic organism just as their "honey urine" attracts ants.

With regard to the part played by malaria, Dr. Severi, Health Officer of Torgiano, Perugia, gave me a very interesting example. He said that in 1880 the Chiagio, a tributary of the Tiber, overflowed its banks and gave rise to a large swamp, which was allowed to stand for over eight years. The swamp brought about the appearance of a prodigious number of toads, which on certain days literally covered the high road to Bettona, and the diligence was obliged to drive over them, crushing thousands of their puffed-out bodies. At the same time, swarms of mosquitoes arose, and malaria broke out and lasted until 1888, when the course of the Chiagio was deviated and the swamp dried. The malaria epidemic was immediately followed by an unprecedented increase in the prevalence and severity of pellagra.

At the Pellagra Congress held at Bologna in 1902, Professor Devoto stated that in Mantua in March, 1901, the Po gave rise to serious inundations, which were followed by numerous cases of malaria and, consequently, owing to lowered resistance, by a notable recrudescence of pellagra.

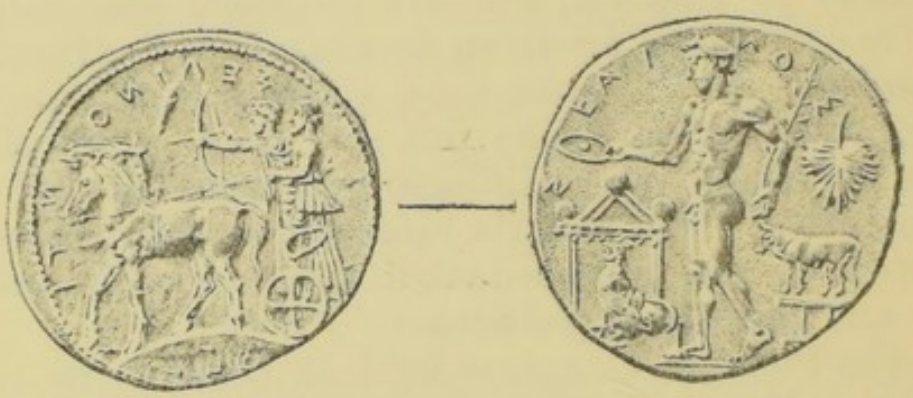
In most of the pellagra districts visited by me, malaria is practically unknown, therefore, only in one case have I been able to observe the co-existence of the two diseases—a well-marked pellagrous rash in a young man who presented a fever of decided tertian type and *Plasmodium vivax* in his blood.

Ankylostomiasis is another affection undoubtedly of importance as a predisposing factor. It is true that ankylostoma eggs are not infrequently found in the fæces of patients presenting only a slight pellagrous rash, but I am convinced that ankylostomiasis, and especially a severe form of the infection, must play a very decided part in the development

of pellagra, as it certainly does in kala-azar, beri-beri, and other diseases.

Topographical Distribution.

The first and most important point to investigate was the topographical distribution of the disease. A knowledge of the exact topographical distribution of any disease of unknown etiology I consider to be the first step towards the elucidation of its cause. In the case of malaria, the knowledge of its swamp origin had from time immemorial focused attention to stagnant water bodies, and already in the fifth



century B.C., a beautiful coin struck by the town of Selinus, Magna Græcia, in honour of Empedocles, records how this great philosopher stamped out the disease by the draining of a marsh. And from the knowledge of its swamp origin arose the mosquito-malaria theory, which, foreshadowed by Columella[1] in the Roman period, suspected by Lancisi in the seventeenth century, propounded by King in 1833,

[1] Columella ("de Re rustica," Book I., Chapter 5) says: "Nor, indeed, must there be a marsh near the buildings, nor a public highway adjoining: for the former always throws up noxious and poisonous steams during the heats, and breeds animals armed with mischievous stings, which fly upon us in exceeding thick swarms; as also sends forth, from the mud and fermented dirt, envenomed pests of water snakes and serpents, deprived of the moisture they enjoyed in winter; whereby hidden diseases are often contracted, the causes of which even the physicians themselves cannot thoroughly understand."

and by Laveran in 1884, was finally established, in 1898, through the genius of Manson, and the labours of Ross, Grassi, and Bignami. In sleeping sickness, the patchy, water-edge distribution of the disease along the banks of rivers and lakes, indicated the tsetse-fly as the carrier, and strongly supported Castellani's discovery of its trypanosomic nature. In the case of pellagra, I felt sure that a correct knowledge of its topographical distribution would at once show whether there was any truth in the maize theory, or whether the disease should be accounted for in some other way.

In Italy several maps have already been published, from time to time, for the purpose of presenting in a graphic form the distribution and prevalence of the disease either throughout the kingdom or in the districts of particular provinces. Such are, for instance, the maps appended to the papers and reports published by Antonini (1895), Sormani (1896, 1902), Cantarutti and Perisutti (1904), Agostini (1904), Zago (1908), D'Ormea, Casati, and Tassinari (1909), Gosio (1909), Terni and Fiorani (1910). A glance at these maps at once shows that only a certain number of provinces are affected, and that in each one of the affected provinces, while some districts are more or less heavily taxed, others are entirely free. And one is struck by the peculiar broken-up distribution of the disease, the immune districts being scattered very irregularly among the affected ones, those adjoining them often presenting the highest incidence.

These maps are not all compiled from the same kind of data, but whilst some are drawn up in accordance with the number of cases reported for each district by the respective health officer, others are compiled from the number of deaths ascribed to the disease or from the number of pellagrous insane admitted from each district into the provincial lunatic asylum.

These maps, being compiled from the available statistical data, which, as we have already seen, are

for the most part inaccurate, must necessarily present the same errors. Therefore it would be unwise to rely upon them for more than a general mandemental[1] distribution of the disease.

At the very beginning of my investigation, in the Province of Bergamo, I discovered a very important cause of error, which vitiates the usefulness of these maps. It was at Castione della Presolana, a mountain district at 870 metres above sea-level, where 90 cases of pellagra had been notified. Here I saw numerous and striking cases of the disease, but I soon found out that most of these cases, if not all, had contracted the infection in the neighbouring Province of Brescia, where the majority of the inhabitants of Castione go twice every year, in spring and autumn, for various field works or the rearing of silkworms. I need but give a few instances :—

(1) Giovanni Ferrario, aged 63, born in Castione, has been a miner all his life, working chiefly abroad. Six years ago he gave up mining, went into the Province of Brescia, and took up agricultural work. There he soon contracted pellagra, and, for five years, the characteristic symptoms have recurred each spring. He now presents marked erythema on face, neck, and dorsum of hands, complains of debility, giddiness and insomnia ; his bowels are usually confined, his mind is slightly confused. He is a man of powerful build and in a state of excellent nutrition. As a child he was reared on maize almost exclusively ; after becoming a miner he fared better. In latter years, owing to more prosperous conditions, his food has been of the best. He drinks coffee in the morning, eats almost every day either meat, poultry or eggs, and always wheaten bread ; in the evening, minestra of macaroni seasoned with bacon fat, sometimes cheese and salad. He drinks good wine, and

---

[1] The "Mandement" is a subdivision of the province comprising several districts.

seldom eats polenta, which is often served at the midday meal for the rest of the family.

This man has two sons, both of whom contracted pellagra several years before him. They both contracted it at the same time in the Province of Brescia, where they both went together to undertake field work, one being eleven, the other nine years old at the time. Both were treated at the pellagrossario of Lovere for two years and recovered. They then returned to Castione, gave up field work, became millers, and are now the picture of health. The wife and daughter, who always remained at Castione, have never had pellagra.

(2) Antonio Tommasini, aged 55, contracted pellagra, in the autumn of 1906, whilst engaged in field labour at Maclodio, in the Province of Brescia. The rash and other symptoms have since recurred each spring. He has eaten polenta all his life. He wife, whom he married thirty-three years ago, has never had pellagra, notwithstanding that she followed him to most places, and frequently worked in the fields with him. Both always fed on the same polenta. They have three sons, all perfectly healthy.

(3) Maria Tommasini, aged 64, has had pellagra for over thirty years. Every year the eruption recurs, usually in May. She contracted the disease near Trenzano, in the Province of Brescia.

I examined a large number of cases in Castione and in the neighbouring villages of Bratto and Dorga, and I found that the pellagrins in these places were for the most part adults, and the majority above middle age. The children were all healthy-looking. Some of the pellagrins I questioned had only quite recently contracted the disease—viz., two, three, or five years ago—others had suffered from it for a very long period of years, even twenty, thirty, or more. In almost every case the date of infection coincided with that in which the patient first went to the Province of Brescia to undertake field labour. In most cases of long duration

reinfection had probably occurred again and again, because the people of Castione and neighbouring places who undertake temporary work in the Province of Brescia continue to do so as long as they are able.

These observations at Castione were made with Professor Balp, Drs. Siler, Perico, and Baldini, in the presence of the local health officer. They showed that this mountain district cannot be regarded as an endemic seat of pellagra, notwithstanding the presence of numerous pellagrins, because the disease is imported and does not spread. Thus Castione della Presolana, which appears as heavily affected in both statistics and maps, should be marked immune.

Of course, for administrative purposes, districts like Castione della Presolana must be credited with the number of pellagrins they are bound to provide for; but, if the statistics and maps are to serve for any scientific purpose, they must be very differently prepared. And, above all, it is necessary to take into account the continual displacements of the peasants wherever such displacements do occur; otherwise, in a disease of long duration, such as pellagra usually is, we are bound to make very serious mistakes with regard to its distribution. Thus, for instance, in provincial maps compiled on the number of lunatics sent from the various districts to the provincial lunatic asylum, we find certain districts marked as intensely pellagrous, whilst on maps compiled from the number of pellagrins reported by the local health officers we find those same districts put down as entirely free from the disease!

At Chiesanuova, Padua, I saw the family Pavinato, consisting of man and wife, apparently healthy, and five children, varying in age from 3 to 12 years, all suffering from pellagra. These children had all contracted the disease at the same time, two years ago, in the Province of Rovigo. But, the family Pavinato had been only seven months st

Chiesanuova (where these five cases had been notified); the year before they had lived at Treponti, also in the Province of Padua; in 1908 they resided in a place called Frasinelle, in the Province of Rovigo; in 1907 they lived at Rosolina; and, in 1906, at Gavello, also in the Province of Rovigo; prior to that, they had been for five years at Villa di Teolo, in the Province of Padua.

Such frequent displacements are exceedingly common in certain districts, and, for this reason, in a large proportion of cases, I found that the disease had not been contracted in the place in which it had been notified.

So long as the maize theory is held to be correct, it matters little where the disease is contracted, but when we repudiate the food theory, and look to the distribution of the disease as a means for the elucidation of its etiology, we need very precise data.

For my purpose it was necessary that I should myself survey the affected districts of several provinces differing, as far as possible, both orographically and climatically; study most carefully every possible detail in the ecological conditions of the disease, and compare the conditions noticed in the endemic areas with those of unaffected localities. My procedure was to obtain from the chief medical officer of each province a general idea of the distribution of the disease within his respective region, then visit the districts most heavily affected, and those returned as absolutely free or only slightly affected.

As soon as I reached a new district, and met the local health officer, the first question was to ask if pellagra was equally distributed throughout his district, or restricted to special localities. The answer was, almost invariably, an enumeration of the localities affected and of those which were not. It was very surprising to find that in many districts, such as Nocera Umbra, for instance, the line of demarcation between pellagrous and non-pellagrous ground

is as sharp as a fence, and yet, hitherto, no one had ever given a moment's thought to this all-important fact in the epidemiology of the disease. It is true that several authors have mentioned instances of two places adjoining, or very close to each other, one of which is more or less heavily affected, the other entirely free, but such instances are cited as mere curiosities without any plausible explanation.

After surveying several districts I became more or less familiar with the nature of the pellagra haunts, so much so that, in Umbria, on visiting new districts, which could be viewed from the commanding height of their inhabited centre, usually perched on a high hill, I ventured to tell the local health officers whence I thought their pellagrins came from, and my guess was invariably right.

Both in Northern and Central Italy I found that the pellagra stations are, as a rule, in the narrower valleys of hilly and wooded country, trenched by swift-running streams infested with Simulium. This is the reason why pellagra is so common among the foothills of the Alps and Apennines, but the disease also spreads out into the plains, following the streams as far as the fly will reach, alternately extending and restricting its domain with the flows and ebbs of Simulium life.

That pellagra is especially prevalent about the lower slopes of mountainous regions was known long ago. Indeed, Pujati (about 1740) gave it the name of "Alpine scurvy," and Sartogo (1791) proposed to call it "mountain scurvy." Odoardi (1776) described it as a disease peculiar to the mountains and valleys of Belluno, and expressed the belief that it would probably also be found in other mountainous countries. Strambio (1794) pointed out that it lurked among the hills of Brianza. And Cerri (1807) stated that pellagra is essentially a disease of the hills and lower mountains.

In all its European centres, whether in Italy,

Portugal, Spain, France, Austria, Hungary, Croatia, Dalmatia, Bosnia, Servia, Bulgaria, Turkey, Greece, Roumania, Bessarabia, Kherson, or Poland, we find pellagra stationed at the base of mountain ranges, along the streams which flow out of the mountain valleys into the subjacent plains.

So far as I know, prior to my papers on the etiology of pellagra, no causal connection was ever suspected by anyone between pellagra and streams of running water, notwithstanding that numerous authors had mentioned the special prevalence of the disease along the banks of certain watercourses. Odoardi (1776) pointed out that pellagra is very prevalent along the left bank of the Piave; Strambio (1794) noticed that it is common "among those who dwell along the River Olona"; Pagani (1806) stated that in Friuli the disease extends along the banks of the Tagliamento from S. Daniele to Valvasone; Arrigoni Degli Oddi (1883) refers to the fact that near Padua the disease has been observed, as a rule, along the course of the canals; Esposito (1902) reports a case from Southern Italy, at S. Stefano, a village placed on the slope of a hill skirted by a rushing torrent, and not far from Nocera Inferiore, where other cases have been observed. Even in other countries the disease has been noticed to prevail along the banks of rivers and brooks. Thus, in Hungary, Dr. Takács (1889) observed it constantly along the banks of the River Szamos in the district called Szilágyság. Quite recently (May, 1910) Professor Alessandrini has confirmed my statement of a connection between stream and pellagra, but he repudiates the hypothesis of an insect carrier, and ascribes the disease to a nematode worm of undetermined genus, which he says he has found in the streams and is taken up in drinking the water thereof. His observations were carried out in Umbria, and more especially in the Districts of Gualdo Tadino and Assisi. "In the

former district," he says, "I was able to notice that the distribution of pellagra is typical and sharply limited by the course of two streams, the Rasina and the Sciola. These, together with the railway line Roma-Ancona, divide the territory into two distinct parts — one mountainous, consisting of the high Apennine mountains, the other all hills. Whilst in the former there are no pellagrins, the latter, in all its fractions (Morano, Cova dell' Occo, Grello, Pastina, Badia, Pieve, San Pellegrino, Piaggie, Poggio Ercolano), is full of them, so much so that all the pellagrins of the District of Gualdo Tadino (254 people: 192 women, 62 men) belong to these fractions. The same may be said to be the case in Assisi, where the fractions most affected are those of the plain and hills."

The first pellagra district I had the opportunity of visiting this spring was that of Trescore Balneario, in the Province of Bergamo, where I went with Professor Balp, Drs. Siler, Perico, Baldini, and Mr. Amoruso. There, the very first pellagrins I was taken to see dwelt along the Tadone, a swift-running stream which flows into the River Cherio. On the slabs and boulders which form the bed of the Tadone we found numerous larvæ and pupæ of at least three different species of Simulium. Two of these, of which we reared adult specimens, were sent to Mr. Austen for determination and were found to be *Simulium pubescens* Macq., and *S. ornatum* var. *fasciatum* Mg.

After that first observation, wherever I found endemic pellagra there also I found both stream and Simulium.

Professor Balp, to whom I had explained my theory, stated that his mind was quite open with regard to the etiology of pellagra, but that he knew of numerous cases of the disease in mountain districts far above any stream. I said those were the very districts I should like to visit so that I might at once

dismiss my theory if it failed to explain satisfactorily the distribution of the malady. Accordingly, Professor Balp took me to Clusone, a small historical town placed on the slope of a mountain, at 648 metres above sea-level. To get to Clusone from Bergamo, one travels by train along the glorious valley of the Serio until one reaches a place called Ponte della Selva, then the road winds up the mountain through a forest of stately pines. Whilst driving up, I said to Professor Balp and Dr. Perico that, judging from the nature of the place, I should not expect to find any pellagra at Clusone. But Professor Balp took out of his pocket-book the official list and said there were no less than eighty-three cases notified. I have already stated that when we got to Clusone we only found a single imported case of many years' standing. At Clusone we partook of luncheon, and when we were served the inevitable "polenta," someone jocosely asked the local physician whether it could be eaten without fear of contracting pellagra. I then ventured to say that the pellagra we had not seen at Clusone would probably be found down by the Serio at Ponte della Selva. Dr. Perico offered to go with me and we soon started down the road that leads to Ponte Briolta, whilst the others followed De Ville who went into the pine forest to shoot woodcock. Dr. Perico and I reached the Serio at a place called Piario. The few houses which form the hamlet seemed deserted, all the good people of Piario were out in the fields with the exception of an old goitrous female of facetious humour who could give us no information. However, in following the stream, we met a young woman carrying a child in her arms, and we found that the child had a typical pellagrous rash on hands and face, though the mother was quite unaware of the nature of the eruption, which she believed to be the redness of severe sunburn. This woman told us of a carpenter of Piario who was known to be a confirmed pellagrin, but we were unable

to see him because, at the time, he was a long way off mending a roof.

The check at Clusone did not disconcert Professor Balp; he owned that, with regard to that place, he had relied on local information, but he insisted that there were other places higher up in the mountains, such as Castione della Presolana, at 870 metres above sea-level, where he had himself not only seen but even photographed numerous pellagrins. Therefore, on another day, we made an excursion to Castione, at the foot of the snow-clad Presolana, and there we certainly did find many cases of pellagra, but as already stated, those we examined proved to be imported cases. However, Castione has its stream of rushing water, the Torrent Borzo, in which Professor Balp was the first to find a few Simulium larvæ.

At Padua, Professor Stefani and Dr. Randi, to whom I also explained my views on the etiology of pellagra, said they doubted whether my theory could hold good in their province, because there were many cases of the disease in the neighbourhood of the town of Padua, but no torrents or swift-running streams, and that the disease was prevalent among the Euganean Hills, a volcanic group noted for the scarcity of water.

The Provincial Medical Officer, Dr. Randi, and Professor Stefani drove Dr. Siler, Mr. Amoruso, and myself to Chiesanuova, where the Local Health Officer, Dr. Carrer, showed us the locanda sanitaria, and then took us round to see the family Pavinato, with five pellagrin children, already mentioned, and another case of a child aged 7, belonging to a family of well-to-do farmers. As we drove along the dusty road which runs in a straight, staring white line along the perfectly flat country, and saw nothing but pools and ditches of stagnant water almost covered with Lemna or Spirogyra, Dr. Siler began to chaff me about my theory. Where was I going to find the howling

torrent, the flying stream, and the ærated-water loving midge? Certainly it was obvious that there could be no roaring mountain torrent in the level Paduan plain, but, perhaps, the pellagra cases notified in that district might prove to be imported cases, or there might be rapidly flowing irrigation canals that we had not yet seen, or, again, Simulium in the choice of its habitat might not always adhere quite strictly to the rules set out in the entomologist's text-book. At the locanda sanitaria of Chiesanuova the commensals we found gathered there were like the commensals of all locande sanitarie, a motley assemblage of poor, sickly creatures, several of whom presented the signs of a pellagra infection of long standing, probably contracted many miles away. I did not trouble about them. With regard to the Pavinato children, I was able to ascertain that they had contracted the disease in the Province of Rovigo two years ago. There remained the daughter of the landed and prosperous farmer. This girl had never been away from the place of her birth, but she lived in a farmhouse inhabited by about a score of people, of whom her mother was the only pellagrin, and had contracted the disease many years ago, possibly elsewhere. It would have been apparently reasonable, therefore, to dismiss this case as one of hereditary transmission, but I am very doubtful about this mode of transmission, and I chose to look upon it as a proof that pellagra is endemic, or at any rate that it is capable of transmission in the District of Chiesanuova.

The day following I had arranged to meet Drs. Lavinder and Blue, who were coming from Milan to see some typical cases of Italian pellagra; I therefore instructed Mr. Amoruso to return very early next morning to Chiesanuova, examine the watercourses of the district, whatever their nature, and endeavour to find me a tube-full of Simulium larvæ by noon, when I expected to reach Chiesanuova with the American colleagues. Pellagra appeared to be

endemic in the district; if this were so, then to the best of my belief Simulium must be present; to him the task of finding it. At the appointed time, on approaching Chiesanuova, I saw Amoruso in the distance waving a test-tube, and I knew that he had been successful. He did not find many larvæ, but he discovered a number of pupæ and empty pupa-cases in sluggish and almost stagnant watercourses. The peasants who watched him collect the cocoons of the tiny aquatic silkworm told Mr. Amoruso that in early spring all the watercourses run far more swiftly.

In all districts comprising both low, flat, or hilly, well-watered areas, and more or less massive mountainous areas, I invariably found pellagra to prevail in the former, and to be absent in the latter. The Districts of Bettona, Ponte Pattoli, and Nocera Umbra may be taken as suitable examples.

Dr. Accorimboni, the Health Officer of Bettona, and a resident since 1888, told me that the mountainous portion of his district is free from pellagra, notwithstanding that the inhabitants are very poor and feed almost exclusively on maize; on the other hand, the disease is prevalent among the more prosperous inhabitants of the lower portion which is watered by numerous streams such as the Chiascio, the Topino, the Ose, the Cagnola, and the Sambro. The Chiascio or Chiagio, as it is also called, is sadly notorious for the number of pellagrous insane who have drowned themselves in its sirenical waters.

At Ponte Pattoli, Dr. Coluzzi told Dr. Lavinder and myself that in his district the disease is confined to the low country on the eastern side of the valley of the Tiber, and more especially to the banks of the Torrent Resina and other small streams, whilst it is unknown in the mountainous parts on the opposite side, such as Mignana di Monte Tezio and S. Lorenzo di Monte Nero. He took us round to see some of the more important cases, amongst whom a poor pellagrous insane, who spent most of her time crying

bitterly for no reason whatever, and then he treated us to a sumptuous repast at his house, where we were served by a pellagrin parlourmaid. When we left in the afternoon, Signora Coluzzi filled our carriage with roses out of her garden, and we appeared as if returning from a battle of flowers rather than from a scouting expedition into the haunts of pellagra.

With regard to Nocera Umbra, Dr. Fattore, who has lived in the district for over fifteen years, informed me that pellagra is unknown in the elevated mountain area, on the right of the Torrent Caldognola where all the inhabitants eat maize of the very worst kind, but prevails extensively in the hilly, wooded region, called "macchia" or jungle, on the left side of the stream. On this side the disease extends all along the Caldognola and its tributaries, being especially noticeable at Villa di Postignano, Castrucciano, Bandita, Lanciano, and Maccantone.

Together with Dr. Fattore and Giacomo Fidato, one of the municipal guards of Nocera, I went to Costapennacchio, a place near Micciano, which the Health Officer considered to be one of the most intense endemic centres. In mentioning this place, I feel I must again express my sincerest thanks to Dr. Fattore who, in order to gratify my eagerness, undertook a long, fatiguing, and even dangerous ride in the pouring rain. I shall never forget the return journey down the narrow, precipitous and slippery paths, over the boggy fields and across the swollen streams, whilst the lightning flashed, the thunder roared, and the rain came down in veritable torrents.

One of the first pellagrins we met on our way to Costapennacchio was Natale Betti, a small, shrivelled-up, and tottery old man who, notwithstanding the disease, is nearing his hundredth year. Further on we saw a young man who wore earings, and had plastered his neck and hands with the leaves of the elder-tree (*Sambucus niyra*) to allay the painful burning of his pellagrous rash. At Costapennacchio

I was introduced to several families, the members of which were all without exception pellagrins. Amongst them were the family Serena, composed of Domenico Serena, aged 49, his mother, his sister Rosa, his wife and two daughters, all pellagrins; and the family Guanciarossa, composed of Angelo Guanciarossa, aged 58, his wife Lucia, aged 48, and three children, all pellagrins.

In the endemic stations I have seen families of no less than eight, ten or more members, all presenting unmistakable signs of pellagra. As an example, I might mention the family Coletti, living in the district of Trestina, at a place called S. Leo Bastia, in the small valley of the Torrent Minima. This family consists of Michele Coletti and his brother Pietro, of Michele's wife, called Diomira, of the latter's father, Ferdinando Ricci, of her three sisters, of her brother, and of her two children, Maria and Dina, all pellagrins. Diomira's mother had died not long ago of pellagrous insanity at the Perugia lunatic asylum. The youngest child, Dina, who was 16 months old in June, had developed a marked pellagrous rash on her face and hands towards the end of March, about two or three weeks after the mother had taken her out into the fields. Diomira said she thought her child must have been bitten by the sand flies which were very troublesome in certain places along the banks of the Minima.

The epidemiological picture of pellagra is in many ways similar to that of malaria, sleeping sickness, Rocky Mountain fever, and other diseases known to be transmitted by mosquito-, fly-, or tick-carriers, presenting well-defined habitats. In non-endemic centres one rarely finds more than one or, at most, two cases in each family or household; the patients are usually adults who work, or have worked, at some time or other, at some distance from home; young children who have never left the place are not affected. In the endemic centres the disease is not limited to a few

adults, but attacks all ages, both sexes, and whole families. Indeed, in certain places such as Costapennacchio, near Nocera Umbra, Paradiso, near Assisi, Villa Pitignano and Cordigliana, near Perugia, Morra and S. Leo Bastia, near Città di Castello, the entire population is branded by the fell disease.

It is a well-known fact, amongst the peasants themselves, that in pellagrous districts the disease is far more prevalent and severe in those who live quite close to a stream than in those who dwell at some distance from it, on the neighbouring heights. At Trestina (Città di Castello), a place I visited in the company of Prof. Centonze and Dr. Sediari, two peasants, Tommaso Perroni and Emidio Caracchini, told me that some years ago they used to live by the Torrent Nestore, but that, owing to the severity of the disease, they had been obliged to abandon their houses near the stream and take refuge, with their respective families, on the Trestina hill. There are places on the Nestore, on the Minimella, and on a thousand other brooks and creeks, where healthy newcomers invariably contract the disease. On several occasions, I have seen families all the elder members of which were pellagrins; whilst the two or three youngest children were not, owing to the fact that the parents had removed from a pellagrous to a healthy locality before the birth of the latter.

At Grumello del Monte (Bergamo) I came across a very interesting case in Rosina Vegis, a woman aged 33, in whom the disease had developed fourteen years ago subsequent to an attack of enteric fever. I examined this patient with Drs. Lavinder and Perico at the Grumello hospital where she had been admitted on several occasions for the same complaint. Dr. Perico and Mr. Amoruso went to the place where she lived and kindly collected for me her history and that of her people. She had a father aged 71, a brother, a twin sister and two younger sisters, none

of whom had ever exhibited any signs of pellagra, notwithstanding that all of them had eaten the same maize supplied by the landowner. Dr. Perico examined the grain and found it to be bad. The only difference between Rosina and her sisters was that, whilst the twin sister and the younger girls had always worked in a textile factory, Rosina had been employed solely in field work, and her principal and daily occupation had been the gathering of twigs for the fire and of leaves for the stable in a neighbouring wood through which runs the Torrent Rillo.

Permanency of Endemic Areas.

If pellagra were really due to the consumption of unsound, imported maize, as generally believed, its distribution would necessarily be constantly shifting with the market distribution of the unsound grain. If, on the other hand, maize has nothing whatever to do with it, and the disease is, as I hold, an insect-borne, parasitic infection, then the endemic centres, or, in other words, the stations of the insect carrier, must perforce continue to be the same year after year, so long as the necessary ecological conditions continue unchanged.

The information already brought forward proves, I think, quite definitely the stability of the topographical distribution of pellagra. Every district health officer who has practised for any length of time in a true pellagrous region, knows perfectly well that, year after year, the new cases occur in the very same localities from which the previous ones came from.

With regard to certain provinces, such as Belluno, Feltre, Padova, Brescia, we possess information which proves that the disease has occupied the same stations for over a century. Thus if we compare the present distribution of pellagra in the Province of Belluno with that observed by Zecchinelli in 1818, and

Odoardi in 1776, we shall find it to be exactly the same. Now, as in 1776, the disease affects the very same places along the valley of the River Piave. For the Province of Padova, if we compare the data published by Fanzago in 1804, with those published by Zecchinelli in 1818 and Degli Oddi in 1883, we shall find that the disease in 1804, 1818, and 1883, affected the same places in the Euganean Hills, in the valleys of Camposampiero, and in the country to the west of the town of Padova in which it now prevails. In the Province of Brescia we likewise find the same distribution of the disease now as in 1837, when it was investigated by Menis. And, at all times, we find the disease presenting the same relative proportion in the various affected regions. Thus, for the Province of Brescia, the order of most to least affected regions is: in 1878, according to Balardini, Verolanuova, Chiari, Brescia, Salò, Breno; in 1890, according to Panizza, Brescia, Verolanuova, Chiari, Salò, Breno; in 1893, according to Maraglio, Chiari, Verolanuovo, Brescia, Salò, Breno; and in 1899, according to Sepilli, Verolanuova, Chiari, Brescia, Salò, Breno.

Exemption of Towns.

Writers are almost unanimous in stating that pellagra never occurs in towns, but is invariably confined to rural districts. A few cases of so-called town pellagrins have been mentioned in literature, but they are exceedingly rare and very doubtful, because it is not likely that these patients had never been out into the country. Marzari (1810) says: "Probably even those cases of civic pellagra which seem genuine are of rural origin. It may therefore be taken as an axiom in medicine that endemic pellagra is absolutely non-existing in towns, but occurs only in rural districts."

Whilst in Italy, I enquired very particularly for cases of town-acquired pellagra, but I failed to find a single example. Dr. Armanni, Health Officer of

Assisi, told me that he knew of two cases, a shoemaker and a mason; the shoemaker was dead, but the mason was still about and doing. I begged Dr. Armanni to endeavour to ascertain whether the mason had not walked out of the doors of Assisi at least once in his life. And the next day I was informed that he had been engaged in building a bridge over a stream the very same season he contracted pellagra.

The exemption of towns cannot be explained by the maize theory, and, indeed, is a very important fact against it. The poor townfolk eat as much maize as the peasants. The zeists say that the townfolk escape because they eat other things besides; but so do the peasants. A further reason submitted is that in towns the grain is of better quality, but the peasants buy their grain in these very same towns.

The absence of pellagra from towns struck me from the first as analogous to the absence of malaria from large towns. Rome, placed in the very heart of an intensely malarious region, escapes the disease. However, in pellagra the limitation is far more definite, because whilst mosquitoes enter houses the sand flies do not. Therefore, while the smaller inhabited centres of malarial regions often suffer very heavily from the disease, pellagra never attacks them.

Limitation to Field Labourers.

Authors are unanimous in stating that pellagra is limited almost exclusively to the field labourer. Already Frapolli (1771), Odoardi (1776), and Gherardini (1780) had stated that it is a disease of the rural population. Albera (1781) found it also in fishermen and in a few well-to-do people. Strambio (1794) says: "Although occasionally well-fed people and town-folk have acquired the disease, nevertheless it is certain that pellagra attacks above all the poor peasant." In all countries where pellagra occurs the same limitation has been observed.

The great majority of pellagrins I had the oppor-

tunity of examining were field labourers, but the disease affected only those field labourers who lived or worked within its endemic centres; the field labourers of pellagra-free localities were never affected, notwithstanding that many of them, especially those inhabiting mountainous districts, were much poorer, fed almost exclusively on maize, often bad maize, and lived in the most insanitary conditions. I must also point out that whilst young pellagrin peasants who give up field labour, some to join the army, others to find employment in towns, often recover from the disease, healthy artisans and fishermen who become farmers almost invariably contract it the very first year they begin to work in a pellagrous district. A good example is that of Giovanni Ferrario, of Castione, who contracted pellagra at 58 years of age, when he gave up mining and took up farming in a pellagrous district of the Province of Brescia.

Occasionally, the disease has been seen in artisans, coachmen, fishermen, and priests. I have seen it myself in shepherds, carpenters, and masons, also in a shoemaker and in a fisherman, but these people lived within the endemic districts and frequently assisted their relatives and friends in field labours when extra hands were required.

The limitation of the disease to the field labourers of pellagrous districts is easily explained by the Simulium theory, whilst no other of the several hypotheses on the etiology of pellagra can account for it satisfactorily.

This peculiar limitation cannot be due to poverty, insufficient nourishment, damaged maize or grinding labour, because as already stated the disease is not found in all field labourers living under similar conditions of destitution, bad food and overwork, but only in those who work within the sharply limited areas in which the disease is endemic. Then again pellagra is known to occur in prosperous farmers and rich landowners. Such cases are not very common, but

they are more frequent than is generally supposed. I have already mentioned several of them myself. The "zeists" have always endeavoured to crush or conceal such cases because they belie their theories and upset their prophylactic measures, but the war against disease cannot be conducted upon the lines of an electoral campaign.

From what I have said it is clear, I think, that the greater liability of field labourers is due entirely to the fact that they are far more exposed to the infective agent than others. Their work keeps them at all seasons and hours, for days together, in the neighbourhood of the swift-running streams which form the characteristic feature of all pellagra stations. Nearly all the pellagrins I have questioned have told me that in spring they are greatly tormented by the sand flies that swarm about these streams. The relative immunity of wealthy landowners, even though they frequently visit their fields, is probably due to the fact that, living at a distance, in towns, they seldom find themselves on the spot in the early morning and evening when the sand flies are most active, and that they are not likely to remain long about the streams, especially when numerous blood-sucking flies are on the wing. The very same fact is observed in malarious regions. Thus, in the deadly Campagna the wealthy landowner who sleeps within the walls of Rome is seldom attacked, though he may frequently visit Ostia or Maccarese in day-time during the epidemic season. Several conditions peculiar to pellagra are also found in malaria, though less marked, because the mosquito is far more ubiquitous than the sand fly. Pellagra is limited to the swift-running stream, malaria to the swamp. Both weigh heavily upon the peasant and both spare the town dweller.

Season of Recurrence and Infection.

Although chronic in its course, pellagra is characterized by a yearly recurrence or recrudescence of its

symptoms. This periodic relapse is best seen in early cases, and is rendered clearly manifest by the pathognomonic rash which appears on the dorsum of the hands and feet, on the face, round the neck, and on the exposed parts of the arms, legs, chest, and back, as also, though perhaps rarely, on the pudenda, scrotum, and perineum. The recurrence of the eruption, with the accompanying symptoms of systemic disorder, always takes place at determinate seasons. It occurs either in spring or autumn, but far more frequently in spring, sometimes both in spring and autumn. In Italy, the spring recurrence usually takes place in March or April, but it may break out as early as February, and the last cases occur about the middle of June. The autumn recurrence takes place in the months of September and October.

I have noticed that in Italy the pellagrous rash appears as a rule somewhat earlier in the central provinces than in the northern ones. Further south, as in Egypt for instance, we find that it makes its appearance as early as January.

Another very interesting observation is that the date of appearance of the eruption varies from year to year in accordance with the prevailing meteorological conditions—the earlier the spring weather sets in the earlier the outbreak of the disease, and *vice versa*. Last spring the weather was exceptionally cold, wet, and cloudy, and most of the patients examined by me stated that their rashes had greatly retarded.

As pointed out by Strambio and others, the pellagrous eruption recurs each spring, even after removal of the patient from the endemic area, and after the entire elimination of maize from the diet. A recent observer, Dr. Warnock (1910), says: "In this Asylum (Abbassia, Egypt) no maize is used in any form. All flour is carefully analyzed, and the diet is kept absolutely free from maize. Yet pellagrous patients resident here for years and thus abstaining from maize

for long periods again develop pellagrous rashes here with acute physical symptoms, sometimes resulting in death."

This recurrence of the eruption each spring in several successive years, with progressive aggravation, in patients who no longer partake of maize or maize products, is a strong argument against the maize theory, since it is a well-known fact that the duration of drug eruptions is always sharply proportionate to the continuance of the exciting cause. Improvement begins immediately upon the withdrawal of the offending agent. Dr. Prince Morrow, in his book on "Drug Eruptions" (New York, 1887), says: "Notwithstanding the diverse character of drug eruptions *they all possess one distinctive generic feature, which stamps them with the seal of a common causality of origin, they always promptly disappear on the withdrawal of the exciting cause.*"

Another peculiar character of the pellagrous eruption is its relation to solar light. Already Strambio had noticed that the rash develops best in full sunlight, and only very slightly or not at all in patients who keep indoors in semi-obscurity. In persons who work in the open the eruption appears on those parts of the body which are bare and exposed to the sun, and when the eruption is actually out, exposure to the sun considerably increases the feeling of burning and tingling in the affected parts.

The pellagrous erythema is not the only eruption the development of which is directly influenced by the actinic rays of the sun. In small-pox, for instance, experience has shown that if the patient is excluded from the short frequencies early enough, the exanthem is lessened and the suppuration prevented. This was known to the Chinese and Arabian physicians, who, centuries ago, employed the red-light treatment for small-pox.

Although exposure to sunlight is certainly necessary for the development of the pellagrous rash, yet we

must not forget that it is only at certain determinate seasons, spring and autumn, that the eruption occurs; and that although clothing has a very marked influence in determining its localization, it can only affect those parts of the body which are its usual seats. Thus Neusser in Roumania saw the erythema only on the hands and feet of gipsy children, though they go about perfectly naked, and Strambio saw it appear on the hands of pellagrins who endeavoured to prevent the blotch by wearing gloves. I have seen myself the erythema on the feet of men and women who habitually wore boots. Finally, we must not forget the occasional appearance of the erythema on the genital parts

So far no one has explained satisfactorily the recurrence of the pellagra eruption each year in spring and autumn, its peculiar distribution, and its relation to sunlight, and yet the key to the whole mystery of the etiology of pellagra lies in this recurrent eruption, and more especially in its peculiar double season of occurrence. Suspecting pellagra to be an insect-borne disease on account of the many analogies of its epidemiology with that of insect-borne diseases, I looked to its distribution, both topographical and seasonal, for the indications that might lead to the discovery of its transmitting agent, and Simulium was found. Pellagra and the sand flies affect the very same topographical distribution, and both exhibit together the same peculiar and unusual double season of activity. And, moreover, the same meteorological conditions which hasten or retard the appearance of pellagra also hasten or retard the active winged- or imago-stage of the Simuliidæ.

The idea that pellagra might probably be an insect-borne disease suggested the presence of a parasite, and probably a protozoal parasite, as its causative agent. Already in 1905, basing myself chiefly on the striking similarity of pellagra to certain diseases of protozoan origin, I suggested for it a similar etiology. Dr. J. H. Taylor, of Columbia, S.C. (1910), has very ably sup-

ported and extended my views on the subject. So far I have been unable to demonstrate any animal parasite, but my researches have been limited to the examination of blood, and that only in a comparatively small number of patients. However, though I have not had the opportunity of carrying out any bacteriological researches myself, I still believe that the causative agent of pellagra will turn out to be a protozoan organism. The disease has none of the characters of bacterial diseases, and many expert bacteriologists, both in Europe and America, have been unable to confirm the findings of Cuboni, Majocchi, Carrariola, and Tizzoni, all of whom have described different kinds of bacteria.

In the peculiar anatomical distribution, seasonal recurrence, and light-relation of the pellagrous eruption, I think we can see a definite correlation between the surmised parasite and the insect which I believe to be its liberating agent and alternative host. The establishment of a definite correlation between the life habits of the incriminated insect and the distinctive characters of the skin eruption will go far towards proving the reality of the parasite and of simulium as its carrier.

We have already seen that there is a perfect correspondence between the seasonal activities of both the disease and Simulium. This fact can only be explained by supposing that the parasites, in pursuance of long-established habit, and stimulated by seasonal influences, moves to the surface at spring time and in autumn, to meet their liberating agent, just as the larvæ of *Filaria bancrofti* periodically swarm, at night time, into the peripheral circulation of their human host to be taken up by the nocturnal mosquito carrier; or, again, as the latent malaria parasites awaken, multiply, and give rise to new paroxysms of fever year after year at the very season of mosquito activity. Several examples might be adduced to show that disease parasites and their transmitting agents are correlated

in as wondrous a way as night- and day-opening flowers, or flowers which give off scent by night or by day with nocturnal and diurnal pollinating insects respectively. And what could be more instructive than the trematode disease of *Succinea putris?* The parasite of this snail attains maturity in the intestine of several Passerine birds. In order that the parasite may develop it is necessary that the snail be eaten by the avian host. To insure this end the trematode sporo-cyst renders the snail very conspicuous by extending its tricolour branches with vivid red tips into the mollusc's tentacles.

It seems to me reasonable to suppose that the erythematous eruption of pellagra is caused by the parasite. We know of several protozoan diseases, such as syphilis and sleeping sickness for example, which give rise to erythematous or papular skin lesions. The contagious character of papular syphilides, at least when they are moist, leads to the conclusion that they represent a localization of the pathogenic agent.

With regard to the peculiar localizations of the pellagra eruption it is interesting to notice that they correspond entirely with those parts of the bodies of animals that are usually attacked by the Simuliidæ—viz., the head, neck, breast, anal region, genitalia, and feet. And from this correspondence I would further infer that probably pellagra is not limited to man, but is also a disease of certain animals, just as Rocky Mountain Fever is not limited to man, but is found in the ground squirrel, ground hog, rock squirrel, chipmunk, and mountain rat. I am led to this belief chiefly on account of the occasional appearance of the pellagrous rash in man about the anal and genital regions observed by Deiaco and Merk.

Having ascertained that the erythema occurs at the very seasons in which the sand fly is active, and assuming that it is caused by a parasite, of which the sand fly is the alternative host, we are led to the conclusion that the eruption period must be at the

same time the season of infection. Now, since we have definitely established that the period of infection does actually coincide with that of the eruption, it necessarily follows that our assumption is correct.

Contagion.

The great majority of authors strenuously deny the transmissibility of pellagra. Their opinion is based on the following facts: (1) The narrow limitation of pellagra in certain centres, often very small, while there is free communication between their inhabitants and the neighbouring population; (2) the almost exclusive limitation of the disease to field labourers; (3) the absolute immunity of urban populations, notwithstanding frequent intercourse with numerous pellagrins from the country; (4) the frequent limitation of the disease to only one member of large families living under the most insanitary conditions and sharing the same bed; (5) the absolute immunity of doctors, nurses, and inmates of hospitals and asylums in which pellagrins are admitted; (6) the non-transmission of the disease from wet nurse to child by means of lactation; (7) the failure of all attempts to reproduce the disease by means of the inoculation of the ichorous matter from the skin lesions or the blood and saliva of pellagrins made by Gherardini (1780), Buniva (1805), De Rolandis (1824), and others.

Other writers—such as Van-der-Heuvell (1787), Videmar (1790), Titius (1792), Zecchinelli (1818), Hameau (1829), Frank (1842), and Botto (1846)—believe pellagra to be a transmissible disease. They point out that, not infrequently, entire families are attacked; that in certain places previously immune the disease broke out after the arrival of pellagrin immigrants; that pellagra everywhere shows a decided tendency to invade new areas, and that in certain years and places it may become particularly prevalent.

Joseph Frank (1842) says he is led to suspect the contagiousness of pellagra because it is not possible to

ascribe the disease either to climatic influences or to special modes of living. Moreover, in view of the fact that it has gradually spread more widely, one must perforce admit that it has some sort of contagious property.

In Italy I found that opinion is almost unanimous as to the non-contagiousness of pellagra. The sick and well are everywhere intimately associated, and nowhere is any restriction placed on the movements of pellagrins. No precautions are ever taken to avoid propagation of the malady in any of the pellagrosari, locande sanitarie, hospitals, insane asylums, and other institutions in which very numerous pellagrins are collected every year. Long experience has taught that there is no danger whatever of transmission from the sick to the healthy in any collective dwelling within urban precincts. In the rural pellagrous districts, however, I did find, both among physicians and peasants, a suspicion that, under certain conditions, the disease might be transmissible.

At Morra (Città di Castello) Dr. Vistoli (the district health officer) and Signor Giuseppe Nicasi (a native of Morra and a member of the local pellagra commission) told me that pellagra broke out at Morra for the first time about twenty-five years ago. The first cases occurred in the family Gianvincenzi, which had always resided in Morra. Four pellagrin daughters belonging to this family married and were taken into the families Franceschetti, Pulcinelli, Dolciami and Alunni respectively. The disease soon broke out in these four families hitherto immune, and subsequently it spread from these to others until almost the entire population of Morra became affected. In the family Betti all contracted the disease early with the exception of the head of the family, who did not work in the fields, but practised in the neighbourhood as a quack doctor. This man kept well until he reached his sixtieth year of age; then he, too, fell a victim to the disease and died of pellagrous insanity. This history of the out-

break of pellagra in Morra was confirmed by the old Archpriest of Morra and by Dr. Antonio Tellarini, of Città di Castello, who told me he had himself examined many of the patients. The very first case of pellagra in the district is said to have occurred in a place near Morra, about the year 1860, and was observed by Dr. Leonardo Speziali, of Lugnano.

The conflict of opinion concerning the contagiousness and non-contagiousness of pellagra is but a repetition of the endless disputation which took place between contagionists and non-contagionists on such diseases as plague, yellow fever, typhus fever, malaria, sleeping sickness, and leprosy. The elucidation of the etiology of most of these diseases, within recent years, has at last settled the question and shown that there was some truth on both sides. In the light of present knowledge, reading the proofs for and against contagion, so ably marshalled by La Roche in his classical work on yellow fever, one cannot help thinking that if the mosquito theory of yellow fever, suggested by Nott in 1848 and again by Finlay in 1881, had been given sooner the serious attention it deserved innumerable lives might have been spared, because all the necessary data were at hand to prove in a most definite manner the *rôle* of the mosquito.

With regard to pellagra, there is no doubt whatever, to my mind, that the disease is an insect-borne disease. Like malaria, yellow fever, sleeping sickness, and other insect-borne diseases, pellagra is not transmissible in places devoid of the necessary insect-carrier; but in its endemic centres, which are also the stations of the Simuliidæ, the disease is highly infectious. Again and again I have met pellagrins who had retired to their native villages in the mountains after contracting the disease in some pellagrous district whither they had gone for work, and yet the disease had never spread from them to other non-migrating inhabitants of the mountain village. On the other hand, I have observed that all those

who go to work during the spring season in one of the endemic seats of pellagra sooner or later contract the disease. Many examples are to be found in literature; I need only mention that of French soldiers who crossed the Alps under the Napoleonic Eagle and contracted pellagra after a short sojourn in the endemic districts of Lombardy. One of them, a man from Brittany, was examined in Paris at the Hôtel Dieu by Hussan and at the Saint Louis Hospital by Alibert.

With regard to lactation, I have been assured by several physicians of wide experience that pellagrin women who take employment in towns as wet nurses never transmit the disease to the children they suckle. Of this fact we can find ample confirmation in literature. Thus Gherardini (1780) states that infants suckled by pellagrin nurses do not contract the disease and grow up perfectly healthy; and Nardi (1836) says: "Although several children belonging to the upper classes of this town (Milan) were suckled by women recognized to be pellagrins at the end of lactation, nevertheless, notwithstanding that some of the nurslings have now passed their fifteenth year of age, not one of them exhibits any sign of having contracted the nurse's disease."

Hereditary Transmission.

A question to which I have devoted particular attention is that of the assumed hereditary transmission of pellagra, because of the bearing it has on the distribution, spread, and prevalence of the disease.

In Italy I found that the great majority of physicians believe most implicitly in the hereditary transmission of pellagra, but whilst some hold that the disease is itself transmitted from parent to child, others believe that it manifests itself in the offspring under various forms of somato-psychic degenerations, or merely as a special susceptibility, a kind of pellagrous diathesis. A perusal of the literature shows a very great difference

of opinion on the subject. Albera (1781) considers pellagra to be hereditary, Odoardi (1776) inclines to the opinion that it may be so, Strambio (1794) declares that he believes in its hereditary transmission because the majority of pellagrins are the offspring of pellagrin parents; because the children of pellagrins are often affected at a tender age; because rarely is a pellagrin found in a family without his brothers and sisters being likewise affected; and because, not infrequently, entire families are affected by the same malady. However, as the children of pellagrins are not all of them invariably attacked, and as the offspring of healthy parents may acquire it, he says pellagra may be both inherited and acquired. Zecchinelli (1818) says: "No one doubts any longer that pellagra is a hereditary disease since it may be clearly seen affecting whole families, more especially within those districts in which it has longest prevailed, as in the districts of Cesana, Limana, Arsiè, Quero, and Alano (in the Province of Belluno). So far, however, hereditary transmission has been observed to occur solely amongst the lower classes, which are everywhere extremely poor. Hitherto, hereditary pellagra has not been observed in prosperous families which have remained almost entirely free from the disease, even though placed in the very midst of the most severely affected populations. If at times a pellagrin has been seen in families not really poor, besides being a very rare case, it was always the only case in the family. For pellagra to be transmitted by heredity it is necessary, even amongst the poorest families, that one of the parents be in the last stages of the disease. And for the disease to be transmitted to newborn infants, it is necessary, indeed indispensable, that the pellagrin parent be the mother, either pregnant or suckling." Lussana (1856), who ascribes pellagra to insufficiency of food, is a strong believer in its hereditary transmission. As an example he mentions the case of a priest of Piazzo Alto (Province of Bergamo) whose

parents were pellagrins. This man lived in perfect health until he was 50 years of age; then, suddenly, he presented the pellagrous rash and other symptoms of the "inherited disease"! Valle, being convinced that food cannot be the cause of pellagra, ascribes the disease to heredity and suggests preventing pellagrins to propagate the species as the only efficient prophylactic measure!

Soler (1791) declares himself doubtful as to the heredity of pellagra, having frequently seen pellagrin mothers with healthy offspring, and the disease affect the children of healthy parents. He considers the disease in the progeny of pellagrin parents as acquired, and says: "Otherwise we should be obliged to admit the absurd notion of a cause in the majority of instances without effect." Facheris (1804) repudiates the idea of hereditary transmission and ascribes the appearance of the disease in the offspring of pellagrin parents to the same conditions of poverty and want of proper food which gave rise to it in the parents. Marzari (1815) states that the disease is not hereditary because he has seen the healthy offspring of pellagrin parents remain always free from the disease. He admits, however, that a certain predisposition to the disease may possibly be transmitted.

The views held now in Italy with regard to the hereditary transmission of pellagra are those of Lombroso and his school. Lombroso (1892) describes two kinds of hereditary pellagra—one very grave, the other very mild. "The first," he says, "manifests itself in the second year; rarely with desquamation, more often with epigastric pain, pyrosis, voracity, uncertain gait, fearfulness, diarrhœa, jaundiced complexion as in malaria, deficient and retarded development, and, at a later period, all the phenomena of pellagra, and an extraordinary tenacity at resisting treatment. In some I found malformation of the skull, extraordinary brachycephaly, or dolichocephaly, retreating forehead, bad setting of the external ears, asymmetry of the face, and anomalies of the genital organs.

"In the same districts in which this form prevails another one also occurs which, though apparently far milder, is even more important to study from the standpoint of prophylactic hygiene. It is a true pellagra sine pellagra. Those presenting this form may exhibit one or other symptom of pellagra, but never so markedly as true pellagrins.

"In the districts of Pazzone, in Venetia, and Favrio, in Trient, I have seen hundreds of these unfortunate beings, some belonging to the better classes, who complained—the men, of burning of the feet, pains in the back, pyrosis; the women, of leucorrhea, feeling of weight in the womb, menopause, eructations, giddiness, constipation, diarrhœa, jaundiced complexion, and yet not one of them had ever presented either desquamation or deliria."

Lombroso is even of opinion that the disease may be transmitted by atavism to the grandchildren. This form of heredity, he points out, very easily escapes the peasant's feeble memory, and yet it is a more important factor in producing pellagra than immediate heredity. As examples of this form of transmission, he mentions the manifestation of the disease in a boy of 12 and in a young man of 18 whose parents were perfectly healthy, but whose respective grandfathers *became affected with pellagra in their old age!*

The symptoms ascribed by Lombroso to his two types of "hereditary pellagra" are in no way convincing, but some of his followers have gone even further astray. Thus Agostini (1904) describes the characteristic features of rickets, myxœdema, and cretinism as distinctive of hereditary pellagra. He says:—

"At the Bologna Pellagra Congress (1902), I described numerous types of heredo-pellagrins presenting the characteristics of simple infantilism, dystrophic and pseudo-myxœdematous infantilism. From the great number of pellagrins examined in the insane asylum of Perugia, and in the pellagrosario of Città

di Castello, I was able confirm the observations of Morpurgo (1891), Buonservizi (1899), Sepilli and Lui (1899), and Antonini (1901), with regard to the inferior physique of pellagrins. In Umbria I have found signs of degeneration in 67 per cent. of heredo-pellagrins, noticing more especially fronto-parietal plagiocephaly, a tendency to hydrocephalus, projection of the frontal eminences, asymmetry of face, projection of cheek-bones, and anomalies of the teeth. Frequently, there is deformity of the vertebral column, of the thoracic cage and limbs. I have often observed hypertrophy and hypoplasia of the thyroid gland which, being particularly susceptible to the effects of the maize poison, must certainly concur in producing the dystrophic and myxœdematous phenomena, and probably aggravating the phenomenology of the pellagra symptoms. Among the types of arrested development due to hereditary pellagra, some exhibit cranio-facial and skeletal changes analogous to those distinctive of rickets; others present the characteristics of true infantilism with or without myxœdema."

Then, after describing and figuring, under the name of heredo-pellagrins, numerous cases of rickets, goitre, cretinism, and other conditions obviously having nothing whatever to do with pellagra, he concludes :—

"*Therefore, whilst in the majority of children born of pellagrin parents, the heredity manifests itself by a reduction of the vital energies, a congenital psychophysical weakness, a development always imperfect and irregular, and a peculiar predisposition to respond to the influence of the pathogenic agent pertaining to the surroundings in which they live, viz., the maize poison; in a certain number of patients the degenerative factor having been accumulated in their procreators, brings about the gravest syndrome of somatopsychical degeneration such as dystrophic cretinoid, and myxœdematous infantilism.*"

The belief that pellagra is a hereditary disease is

untenable now that we know that diseases are not hereditary in the scientific sense of the word "hereditary." There is no hereditary small-pox, no hereditary tuberculosis, no hereditary syphilis, and likewise there can be no hereditary pellagra. Whether pellagra may be acquired *in utero* by means of placental or amniotic infection is a different matter. Several authors have reported the disease in "newborn" children, but no one has ever described a case in which the infant was born with the characteristic signs of the disease upon it. I have no reason to doubt that pellagra may be acquired *in utero*, but I have never seen a congenital case myself, nor have I ever heard of one. According to my experience, antenatal pellagra, if it does occur, must be exceedingly rare. Within the endemic areas, pellagra affects entire families and, as might be expected, the disease is very common in young children and infants, but in such places the children are exposed to the very same influences which engendered the disease in their parents, blood collaterals and ancestors. In non-endemic areas, such as Castione della Presolana, in the Province of Bergamo, notwithstanding the presence of numerous pellagrins, I was unable to find a single case of the disease among the younger children, whether their parents were pellagrins or not. I examined with special care the children of families in which both parents were pellagrins and had contracted the disease before the birth of the children, but I was unable to detect any sign of the disease in the offspring. Indeed, these children differed in no way from the children of non-pellagrin parents living in the same locality.

Both physicians and peasants told me of pellagrins whose elder children, born in a pellagrous district, were also pellagrins, whilst the youngest, born after removal to a healthy locality, were entirely free from the disease. On the other hand, it has frequently happened that in a family the four, five, or more

healthy children born in a pellagra-free district suddenly acquire the disease all at the same time on taking up residence in a pellagrous locality. I have already mentioned the example of the family Pavinato, in which five healthy children simultaneously contracted pellagra on removing to Frasinelle, in the Province of Rovigno. Another well-attested fact is that children sometimes become pellagrous first, their parents afterwards. Thus the two sons of Giovanni Ferrario, of Castione della Presolana, contracted the disease in the neighbouring Province of Brescia several years before their father, for the simple reason that they both went to work in an endemic locality several years before their father. Although children are very frequently affected, I have often seen patients upwards of 80 years of age who had been pellagrins for two or three years only. Thus Placido Ferrari, of Castione, 81 years of age, contracted pellagra three years ago in the Province of Brescia soon after taking up field work, which he had never done before. He has always fed on polenta and cheese. His family consists of eight members but he is the only pellagrin.

With regard to any form of degeneration peculiar to the progeny of pellagrin parents, I must point out that within the affected districts pellagra is not the only disease prevalent, and that the adult pellagrins may also be tubercular, syphilitic, or alcoholics. In several places I have found ankylostomiasis to be very common; in others goitre and cretinism. These and other diseases which are known to cause striking degenerative changes must not be overlooked. I do not wish to infer that pellagra may not itself give rise to some kind of degeneration, but my view is that the degeneration is more likely to be the consequence of impeded development in children early attacked within the endemic centres of the disease than the result of a hereditarily transmitted unknown element.

Correlation between Epidemic Season and Age of Infection in Infants.

I endeavoured to find out whether there was any correlation between the date of the first appearance of the disease in infants under eighteen months and the season in which the disease prevails. I found that infants are attacked between the ages of three or four months, when, as a rule, they are taken out into the fields; and fourteen or fifteen months, according as they are born nearer to, or further from, the epidemic season to the infective agencies of which they may be exposed. Thus, an infant born in November may contract the disease as early as the fourth month, because it is likely to be taken out into the fields at that age during the next infective season, February—May. But, if it be born in April, March, or even February, it is almost certain to escape infection during these infective months, owing to non-exposure, and, in that case, it cannot become infected until the following infection season; therefore, only twelve to fifteen months after birth.

At the pellagrosario of Città di Castello, June 2, Dr. Fabbri showed me a pellagrin infant, the child of Veronica Pierni, herself a recent pellagrin, living for the past two years at Passano, near to the stream of the same name. The infant was born in November, 1909; it was taken out into the fields about the middle of March, and the mother told me that, after suckling it, she used to arrange it comfortably in a corner of the field, and leave her 5-year-old boy to watch over it and keep off the sand flies, whilst she attended to her work close by. In the following May the infant developed a marked pellagra rash.

At S. Leo Bastia, a small village on the banks of the Minimella, I examined the family Ricci, composed of eleven members, all pellagrins. The youngest is Dina, an infant 16 months old. This child was born in February, 1909. Owing to the mother's health and other circumstances it was not taken out until May,

and escaped infection during the pellagra epidemic season of 1909. This spring the mother took it out with her into the fields, and in the first days of April the child presented a typical pellagrous eruption on face and hands. The mother, in answer to my questions, said the sand flies were numerous and troublesome by the stream, and that the child may have been bitten about the head, which was unprotected.

At Morra, on the Torrent Nestore, together with Dr. Centonze, Professor Pisenti, Dr. Tellarini and Dr. Vistoli, I saw Eugenio Corneli, aged 44, and his family, composed of wife and five children, varying in age from fourteen years to four months. All were pellagrins except the infant—which was born in February and looked the picture of health. The eldest child, Angela, had contracted the disease when 12 months old, and she was likewise born in spring.

At a place called Pugliola, on the Torrent Puglia, in the district of Colazone, Perugia, Drs. Magnini and Lupatelli showed me a boy aged 8, a poor little stunted and anæmic bastard who was born in prison, his mother being implicated in a murder committed by the man she was living with. The mother was allowed to suckle her babe, in prison, until it was 5 months old : then, one March day, it was taken away from her and entrusted to peasants who live at the Pugliola. Here, in about two weeks, it developed pellagra. Now, besides pellagra, the poor boy has ankylostomiasis, and a few days before our visit he had passed a number of eelworms.

Incubation Period.

Sandwith (1905) and Merk (1909) are the only authors, to my knowledge, who speak of the incubation period of pellagra. Sandwith says: "It is difficult to fix any incubation period because the onset of the disease is so insidious. But it is perhaps worth referring again to the fact that the maize crop in lower Egypt is harvested in November or December and that

the bulk of the patients seem to begin their eruption in January. It is unlikely that the November crop could become so poisoned by the fungus as to produce a skin eruption in January after, presumably, an intervening period of premonitory symptoms. I think we must, therefore, assume that the eruption is the result of poisoning from the previous year's crop or, in other words, that incubation is perhaps from nine to twelve months' duration."

Merk says: "The appearance of the erythema depends solely on the eating of maize, and I believe I can state from actual observation that it does not break out until from seven to nine months after."

I need hardly point out that the above statements are entirely hypothetical and based on the erroneous assumption that maize is the true cause of pellagra. My own observations lead me to believe that the incubation period of pellagra is a short one. In the first place, I have seen the disease in infants from 4 to 5 months old; it is evident, therefore, that the period of incubation in these cases could not have lasted longer than five months, but the infants were born, some of them in November, others in December—that is to say two and three months respectively before the onset of the season in which infection is possible. This reduces the duration of the incubation stage to two or three months. Finally, the infants had not been taken out into the fields earlier than two or three weeks before the appearance of the erythema, which shows that in all probability the period of incubation had not lasted longer than three weeks, admitting that the infant had contracted the disease on the very first day of exposure.

It might be objected by some that the appearance of the disease at so early an age might not be the result of an acquired infection, but the evidence of hereditary transmission. That such an opinion is inadmissible is shown not only by the fact that, so far, the hereditary transmission of the disease itself is

neither proved nor believed in, but also by the fact that two of the infants presenting the characteristic erythemata at the fifth month from birth were born of non-pellagrin parents.

In adults it is as a rule very difficult to determine the period of incubation, especially when they have lived from childhood in a district including pellagrous areas. They invariably overlook the disease during the first years when a mild sun-burn-like erythema is the only characteristic symptom.

Duration of Disease.

Pellagra may run a rapid course and end fatally in from two to three years, but, as a rule, it is a disease of long duration. When mild and uncomplicated, it may last a great number of years. I have seen many patients who declared that they had suffered from pellagra for twenty, thirty, and more years; others of upwards of 80 years of age claimed to have been pellagrins since early childhood. At Acquiniano (Nocera Umbra), Dr. Fattore showed me a pellagrin, aged 99, and Dr. Armanni told me of a pellagrin woman, in a small mountain village near Assisi, who was 102 years old, and whose hands still donned the pellagrous bloom at spring time.

Probably, in a number of cases reinfection is the cause of long continuance and aggravation. Indeed, patients removed from the endemic centres improve very rapidly, whilst those who continue to live within the infective area become, as a rule, every year more heavily affected. In pellagra, as in beri-beri and malaria, a change of residence from the infective centre to a healthy locality is a most essential step towards recovery.

Strambio (1794) has proved that good food continued for several years does not entirely overcome the disease, not even in patients of recent infection. He says:—

"I have purposely retained in hospital some pella-

grins of the first stage for two, three, and even four years, feeding them with all the liberality allowable in such institutions; they gained in strength, and some of them fattened considerably, but always there remained in them some evidence of the latent malady. Although improving considerably in winter, each spring they exhibited some amount of deterioration; exposure to the sun brought out a rash on the back of their hands: indeed, by degrees, notwithstanding the good feeding, the disease advanced into graver stages and finally terminated in death. This clearly proves that good nourishment may conceal the disease and retard its progress, but is unable to destroy the cause and reintegrate the fluids of the body once they are deteriorated.

"Giovanni Parini of Lainate seemed to have thoroughly recovered from the disease, but after again working in the fields he returned to hospital in a more serious condition than before. Having once more recovered, I purposely retained him as hospital attendant in order to ascertain whether a definitive recovery could be obtained by means of long-continued good feeding and non-exposure to the sun. Assuredly, he did keep well, and showed so much energy in the carrying out of his duties that when this hospital was closed at the end of 1788, I found him another post at Monza. There I saw him in the summer of 1792; he looked healthy, bright, and of good colour, but the giddiness he suffers from at times, and a slight redness I noticed on the back of his hands, make me fear that even now there is a snake in the grass, and that if he were to return to his former rural occupations, once again he would sicken as before.

"The same thing I have observed in a certain Rosa Olgiati, of Legnano, whom I also retained for some time as nurse, and subsequently placed in a home for poor women. It is true that she does not suffer from the disease as formerly, but she still exhibits unequivocal signs of its presence."

The admirable and trustworthy observations of Gaetano Strambio the elder, and the experiment carried out by Cerri in 1795, on behalf of the Lombard Government, show how little we may trust the miraculous cures of the locande sanitarie and pellagrosari of the present day.

Statistics.

In discussing the various measures ordered by the law of 1902, I assumed for the moment that, as indicated by the official statistics, there *had* been a decline in the prevalence of pellagra between 1902 and 1909, and I endeavoured to show that, owing chiefly to their limited application, these measures could not possibly have exercised any appreciable influence on the prevalence of the disease. But has there really been any decline? To this question I am bound to give a negative answer.

From what I have said previously with regard to the notification of cases it is quite obvious, I think, that the statistical data concerning pellagra must be grossly erroneous. My own observations made in the presence of highly qualified witnesses have proved it over and over again. If this be so, now that the notification of cases is compulsory in all pellagrous districts, what reliance can be placed on data collected previously to 1902, and what can be the use of comparing the erroneous figures of the latest pellagra census with the figures still more unreliable of previous censuses?

I believe I can state, without fear of erring, that pellagra now, as in the days when Frapolli first recognized it, occupies in Italy almost everywhere the same areas, fluctuating in prevalence from year to year with the more or less favourable ecological conditions. Like malaria and other insect-borne parasitic diseases, it has its alternate periods of slumber and activity.

Badaloni, speaking in the Italian Parliament on

March 3, 1908, said: "It is stated that pellagra has greatly diminished in Italy. But I have no great faith in the accuracy of this assertion, and there are many reasons which incline me to hold the contrary opinion. However, it is a certainty that, if you base your estimate upon the statistics concerning the number of individuals to whom are extended the benefits of those measures that weigh upon the budgets of the communes and the provinces (and they are strictly accurate statistics) you may find reasons for the support of the belief that pellagra is greatly declining."

Hæmatology.

Owing to lack of suitable pathological material, laboratory accommodation, and time, my microscopical researches have been somewhat scanty and unsatisfactory. The principal object of the expedition to Italy was the study of the epidemiology of pellagra. But I lost no opportunity of examining the blood in typical cases, and thus I was able to examine hundreds of fresh and stained smears from over sixty typical cases. However, so far, I have been unable to find any parasite (either protozoon or metazoon) that might account for the disease.

With regard to the blood itself, the results of my examinations are somewhat at variance with those of certain Italian observers, and this is not surprising, because I limited my examinations to patients, chiefly children, presenting a characteristic rash in the acute stage, whilst other investigators examined old chronic cases, and, judging from their diagnostic views and the result of their examinations, it is even doubtful whether all their patients were true pellagrins or, at any rate, uncomplicated cases of pellagra. Thus Agostini, who appears to confound rickets and cretinism with pellagra, speaks of pallor of red cells, slight tendency to rouleaux formation, abundant small cells (?), poikilocytosis, large leucocytes with large granules (?), and abundant pigment (?). And Masini (1900) mentions

a constant and conspicuous eosinophilia, which he suggests may prove a valuable aid in early or differential diagnosis!

I have not found any marked increase of eosinophiles except in cases complicated with ankylostomiasis or other nematode infections. The only characteristic feature appeared to be a relative increase of the mononuclear leucocytes.

Dr. Low, who has examined the blood of a pellagrin I brought to London and numerous films prepared in Italy from the blood of other typical cases of the disease, has kindly sent me the following preliminary statement:—

"The blood in pellagra.

"A complete blood-count of a girl aged 14—a typical case of pellagra—brought to London by Dr. Sambon, gave the following result:—

Red cells	4,850,000
White cells	8,400
Hæmoglobin	95 per cent.

Differential leucocyte count:—

Polymorphonuclears ..	56	per cent.	500 counted.
Large mononuclears ..	4	,,	
Lymphocytes	37·6	,,	
Eosinophiles	4	,,	
Transitionals	2	,,	
Mast cells	0		
	100		

"The shape and size of the red cells were good. No parasites of any kind whatsoever were noted in the blood. In the differential count it will be noted that the lymphocytes (by that meaning small lymphocytes) are relatively increased.

"This latter condition, a relative increase of the lymphocytes, was further borne out by a series of fifteen differential counts (500 leucocytes in each case) from different cases the blood of which was brought by Dr. Sambon from Italy. In most of these

this was present, and where it was absent there was generally something to account for it, such as a polymorphonuclear leucocytosis due to sepsis or relative increase of the eosinophiles, in all probability due to ankylostomiasis.

"The large mononuclear cells (by this meaning the type of cells usually seen in cases of malaria) were normal or diminished, certainly never increased. The cases where eosinophilia was present all came from an area where ankylostomiasis was prevalent, and this in all probability accounted for it.

"The changes found, then, in differential counts of the leucocytes in pellagra cases may be summed up as follows: In the majority of cases a relative increase of lymphocytes is present; there is no change in the large mononuclear percentage.

"No parasites of any kind were found in any of the specimens of blood examined, this bearing out the work done by others. Special attention was directed to the possible presence of spirochætes, a modified Indian ink method and other stains being employed; but the results were uniformly negative. Nothing of the nature of trypanosomes or other protozoal parasites were ever seen.

"In several thick films of dry blood the hæmoglobin was washed out, and the film was stained for filariæ. The results again were negative.

"There would seem, therefore, to be little to be gained from the examination of the blood in pellagra, but the failure to find any definite microscopical parasite does not, of course, exclude some ultramicroscopical germ as probably being the cause of the disease (compare yellow fever, dengue, &c.)."

The Insect Carrier.

As already stated, it was the peculiar topographical distribution of pellagra and the extraordinary fact of its double seasonal incidence which led me to think that Simulium might possibly

be its necessary transmitting agent. Having never seen a Simulium, I went to have a look at the specimens in the British Museum, and Mr. E. E. Austen kindly placed at my disposal all available material and information, and showed me also some Simulium larvæ, the only ones in the Museum, which had been collected not directly from a stream, but from the stomach of a trout.

In Italy, having found Simulium in the Tadone, and subsequently in all the streams of pellagra districts, I at once adopted a severely critical attitude towards the Simulium theory. Together with Mr. Amoruso, who devoted all his time to entomological field work, I endeavoured to find out whether any other blood-sucking arthropod could be discovered which might explain the peculiar epidemiology of pellagra; but we failed to find any. In the Province of Bergamo, where we worked from March 26 to May 9, we only found a few hibernating mosquitoes in the houses, and *Stomoxys calcitrans* in the stables. These insects, on account of their well-known life habits and because they were found in a few localities only, may be discarded. The common stable-fly, however, received some attention, owing to the fact that the peasants of the northern provinces of Italy spend most of their time in the stables, especially in winter, for warmth. I often found the women spinning and the children playing in the stables, and once I saw a boy, suffering from enteric fever, lying with the cattle in a small, dark, ill-kept stable with only a tiny window in a corner, plastered over with cow-dung to keep the air out. All the stables were heavily curtained with spiders' webs, and when Dr. Perico remonstrated with the peasants on account of the filthy condition of their cobwebbed stables, they answered that the cobwebs were essential to the healthiness of their cattle. This we found to be a general belief amongst the peasants, who seemed very unwilling to brush away the dust-laden sheets of

Arachne's weave. We laughed at their superstition, but I soon found out that the laugh should have been on their side. At Comun Nuovo I visited the Cascina Benaglia, a kind of model farm. Here there were hardly any cobwebs, because the ceilings were frequently swept. But the walls of these stables were literally covered with hibernating stable-flies. Thousands could have been collected in a few minutes. A few spiders were busy amongst them, abstracting the blood on which the latter had gorged. Then I understood why the farmers leave the cobwebs, and I said to Dr. Perico that I should not be surprised if anthrax were to break out amongst the cattle of the Benaglia farm. I also advised a thorough fumigation of the stables in early spring to kill off the hibernating flies. Curiously enough, about ten days later Dr. Perico informed me that two of the cows of this farm had died of anthrax. I at once despatched Mr. Amoruso to collect some of the flies alive for bacteriological investigation, but he arrived too late; my suggestion had been carried out by order of Dr. Perico, and there was not one fly remaining. Mr. Amoruso then went with the local veterinary surgeon to other stables, where cases of anthrax had occurred the year before, and there collected a number of flies. These were sterilized externally in the flame of a spirit lamp, then heads and bodies separately were emulsified in normal salt solution, and cultures prepared in various media. These were left to Dr. Minelli, bacteriologist to the Bergamo hospital, who also kindly undertook to make inoculations in animals. But the results must have been negative, as we heard nothing more about our cultures, and when we returned to Bergamo Dr. Minelli had left.

Large numbers of spiders were collected in the stables by Dr. Perico, Mr. Amoruso, and myself, and the following species were found: *Amaurobius ferox*, Walck; *Pholcus phalangioides*, Fuessler; *Theridion tepidariorum*, C. Koch; and immature specimens of

a species of *Tegenaria*. They were kindly determined by Mr. A. S. Hirst, of the Natural History Museum.

Simulium larvæ were found to be extremely abundant in nearly all the streams of pellagrous districts, but their distribution along the course of the streams was very irregular. In the notes on Simuliidæ appended to this report will be found all the observations I have been able to make on the distribution, life habits, and natural enemies of the Simuliidæ in Italy; here I will only refer to their connection with pellagra.

On account of their great numbers in all pellagra stations, the sand flies are well known to the peasants, who call them "moscerini," "moschini," or "muffini." The following are a few of the notes on these insects gathered from pellagrin peasants themselves.

At Trescorre (Bergamo), Angelo Caldara, aged 56, and born at Lussana, said he had been at Trescorre twenty-seven years, and had always worked near the Torrent Tadone. He contracted pellagra the second spring after arrival. He had frequently noticed the "muffini": they appear in spring on the first sunny days, they fly straight in one's face, bite fiercely in the fields, but they never come into the houses like flies and gnats do.

Maria Fachinetti, a washerwoman, aged 50, contracted the disease eight or ten years ago; the eruption recurs each spring on hands and feet; she complains of headache, giddiness, and insomnia. Whilst washing clothes in the Torrent Tadone, she was frequently assailed by the "moscini," and their bite gave rise to such intolerable itching that she was obliged to scratch the parts until they bled. This occurred in spring and sometimes also in autumn; never in summer.

At Castione della Presolana, Antonio Tommasoni contracted pellagra four years ago at Maclodio, in the Province of Brescia. The disease manifested itself first in autumn. At Maclodio he was frequently

bitten by numerous "moscini" whilst working in the fields near running water.

At Bettona (Perugia), Giuseppe Scardazzi, aged 60, contracted pellagra over twenty years ago. The erythema occurs every spring and autumn. It comes on suddenly, and gives rise to so intense a feeling of burning that he is obliged to poultice his hands with the leaves of the elder tree. The eruption, he says, looks exactly like a scald. He complains of vertigo and exhaustion. He has never moved from Bettona, and has always worked by the Torrent Sambro. He says the "mosciolini" appear in swarms like bees, they bite chiefly on the face, round the eyes, and they often penetrate into the nose, ears, and mouth. Then bite in the morning at sunrise until 8 or 9 a.m., they again in the evening at sunset. During the heat of the day they are seldom about. They never come into the houses; one may encounter them on the road, but they are usually in the fields in the neighbourhood of streams.

At Pomonte (Perugia), Paolo Fontetrosciano, aged 67, contracted the disease about twenty year ago. He works alongside the stream. The eruption appears in March and lasts until June. Sometimes it recurs in autumn, but is then of short duration. He says that the "moscerini" appear in spring. When the weather is warm they appear in March, April, and May. On the advent of cold weather they disappear. They are a fearful pest in the fields. They never enter the houses. They are most active early in the morning before sunrise; never during the hottest hours of the day. They are very troublesome in the evening by the streams.

Letizia Morelli, aged 53, is a pellagrin of twenty years' standing. The eruption recurs each year in March; it affects her hands, her feet, and also, slightly, her face. She is troubled by copious salivation. She has not eaten maize for at least two years. The "moscerini" have bitten her very fre-

quently whilst she has been engaged in gathering wood by the streams. Their favourite time of attack is a cloudy day.

At Morra, the peasants told me that the sand flies often appear in great numbers and form regular clouds. They bite especially in the evening, but on dark, cloudy days also in the daytime. They are most abundant in the latter part of May and the beginning of June. In favourable weather they begin to appear in March and April. They are never seen in August. They are found in the neighbourhood of streams, rarely along the roads. They never enter houses.

At Trestina, Emidio Caracchini, a pellagrin of twenty years' standing, states that he has been bitten very frequently along the Torrent Nestore. The "moscerini" appear in April and May, sometimes also in March. They bite in the evening, usually about the face; they are always near the stream, especially in localities with dense thickets of underbush. At times they are so troublesome that the labourers are obliged to discontinue their work.

At Busa (Padua), Silvio Libero, aged 38, contracted the disease in childhood. His father and his four children are also pellagrins. His wife died of the disease about two years ago. He tells me that the "moschini" are very numerous and very troublesome where he works. They bite on the back of the hands, on the face, in the ears, about the eyes, and also on the feet, when bare.

Although I found numerous species of Simulium larvæ in the streams, I was only able to collect three species in the imago stage; and one of these—*Simulium ornatum*, Mg.—was obtained by Mr. Amoruso from pupæ collected in the Torrent Tadone at Trescorre.

The difficulty of obtaining adult specimens was due to the continued rains. Only on May 23, along the Ose, a stream near Castelnuovo, Assisi, were we able to collect large numbers of female specimens of *S. pubescens*, Macq.

My specimens have been identified by Mr. Austen,[1] who has kindly sent me the following statement :—

"With the exception of a single denuded specimen of *S. reptans*, L., all of the perfect insects of Simulium brought home by Dr. Sambon belong to two species, both of which are found in Great Britain, *S. ornatum*, Mg., var. *fasciatum*, Mg., and *S. pubescens*, Macq. Out of twenty-four specimens all but three belong to the latter species, about which little or nothing has hitherto been published, though it was described so long ago as 1834 ; it has, however, in recent years been taken at Christchurch, Hants. *S. ornatum*, which is generally distributed in Europe, is fairly common in Great Britain, from the north of Scotland to the south of England ; in Italy, according to Professor Bezzi, it is common near Pavia, even in winter."

A fact which has an important bearing on the connection between the Simuliidæ and pellagra is that of the increase both in the prevalence of the disease and swarming of Simuliidæ following upon inundations. Thus in the autumn of 1872 a considerable increase of pellagra followed a severe inundation which covered one third of the Province of Mantua. The same thing occurred, according to Balardini, after the floods in the Pavese and Lodigiano districts in 1839. Also in the Province of Venice it has been noticed by Lette that the most fruitful pellagra years were always those with rainy and cold autumns. Dr. Magnini told me that in his district the heavy rains and overflows of 1896 were followed by a considerable increase of pellagra in the spring of 1897. The Italian authors ascribe this increase of the disease to some extent to the squalor and misery following the inundations. In the Simulium theory, however, this fact finds a very striking explanation. It is well known that inundations are followed by a great increase in the numbers of Simuliidæ. This connection has been

[1] So far Mr. Austen has only determined the few specimens that Mr. Amoruso had time to mount.

observed again and again in the Mississippi regions with regard to the buffalo gnat; in Hungary, along the Danube, in connection with *S. columbaczense;* and in all other regions where Simuliidæ are found.

That Simulium is found, and abundantly found, in all pellagrous districts throughout Italy, is a fact which I have thoroughly ascertained; indeed, the only objection which might be brought against the Simulium theory of pellagra is that Simulium is also found in places where there is no pellagra. This is exactly what should be expected. There are plenty of non-malarial places in Europe where *Anopheles maculipennis* abounds. England may be taken as an example, and a most excellent example, since in days gone by the disease was greatly prevalent in the fen districts of Cambridgeshire, Lincolnshire, and in other parts. Filariasis is another disease the distribution of which is far more restricted than that of the mosquitoes which subserve its maintenance and dissemination. The difference between the restricted distributional areas of yellow fever and the world-wide dissemination of *Stegomyia calopus* is an example even more striking, but many more might be adduced, and, indeed, it appears to be the general rule that the carrier is more widely distributed than the germ. With regard to the Simuliidæ and pellagra, I must point out that there are many species of Simulium, and that possibly only some of them play any part in the transmission of the disease. In the malarial fevers of Europe we know that not all mosquitoes, but only certain species of the sub-family *Anophelinæ*, are capable of transmitting the infection.

Many other conditions might account for a difference in the distributional areas of pellagra and Simulium, but in the first place we should ascertain the exact ranges of the disease and of the various sand flies.

Another objection which has been raised by some is that in certain countries—as in Egypt, for instance, the West Indies, and certain parts of the United

States, where pellagra is rife—there are no Simuliidæ. A similar objection was made to the mosquito theory of malaria. I remember that someone said the theory would not hold good for China, because there were no mosquitoes at Hong Kong! The Simuliidæ have a world-wide distribution, and, knowing the topographical conditions peculiar to pellagra, I have no doubt whatever that where there is pellagra there sand flies will also be found. With regard to the Nile Valley, I know that Simulium is found in the region of the cataracts, and I have no doubt it will also be found at Zagazig. Only a few days ago Colonel Alcock showed me three species of Simulium sent to him by Dr. Johnston from Jamaica, and Captain Siler writes me that in the United States Simulium is being found wherever there is pellagra.

From the very first my theory on the etiology of pellagra has received the support of competent authorities. Thus Sir Patrick Manson did me the honour of endorsing it in the last published edition of his text-book on Tropical Diseases, and Castellani and Chalmers uphold it in their recent Manual of Tropical Medicine.

At the third Pellagra Congress, held in Milan in 1906, Professor Terni said: "None of the theories so far advanced furnish in a satisfactory way the data required by science to consider the causation of pellagra as established and proved. Therefore its solution must necessarily be expected from future researches. With regard to this, I am rather inclined to agree with the opinion recently expressed by Sambon, who believes that the causative agent of pellagra may be a protozoan organism, because there are many points of similarity between the clinical picture of this disease and that of other protozoan diseases, such as kala-azar and beri-beri, at one time likewise believed to be food diseases."

At the Pellagra Conference held in Columbia, U.S.A., on October 29, 1908, Drs. Moore, Wood and Taylor

spoke in favour of my theory. Dr. Wood said: "I think we will all agree with Sambon in considering that pellagra, both in its symptoms and pathology, is allied rather with syphilis and trypanosomiasis than with a fungus disease. The sooner we dispel the idea that pellagra belongs to the ergot group of diseases, the sooner will we clear up the question of its etiology."

At the National Conference on Pellagra held in Columbia, S.C., November 3 and 4, 1909, Dr. Taylor said: "In considering the glaring incongruities of the maize theory of pellagra, the striking and distinct periodical appearance of the skin symptoms, a phenomenon incompatible with toxin poison of the maize type, and its striking similarity to certain diseases of a protozoan origin, Sambon has mentioned as possible a similar etiology for it. This suggestiveness runs throughout the entire symptomatology, pathology and treatment of both syphilis and sleeping sickness, or trypanosomiasis, both protozoan diseases, and the Wasserman reaction justifying us in considering general paresis and tabes dorsalis as syphilitic manifestations, we include these under this head."

Professor Babes, the eminent Roumanian physician, and hitherto one of the staunchest supporters of the maize theory of pellagra, has quite recently embraced my theory. In 1901, in Nothnagel's System of Pathology and Treatment, he declared himself a convinced zeist, stating that "Pellagra must be looked upon as a chronic and periodically recurring intoxication-disease caused by a specific, poisonous substance produced by more or less spoiled maize, which, if used continuously and in large quantities, affects in a peculiar, harmful way the nervous system." In 1909, he says: "From its analogy to malaria, piroplasmosis, and trypanosomiasis, diseases to a certain extent with the same geographical distribution, the thought is justified that for the transmission of pellagra some similar, intermediate animal host is necessary; and

for the intoxication or infection itself some microscopic animal parasite. Such a parasite must necessarily be very minute, perhaps ultramicroscopic." He further mentions the finding of bodies resembling the smallest Negri bodies in the erythematous skin of pellagrins, and concludes that the beneficial results of arsenical treatment, the almost specific therapeutic action of which is now well known in the treatment of other protozoan diseases, encourage new investigations along the lines suggested."

Finally I have received valuable support in my investigations from Dr. Sandwith, who not long ago looked upon a failure to accept the corn theory *in toto* as evidence of insufficient study of the subject.

So far the only criticism adverse to my theory is that of Captain H. J. Nichols, U.S. Army, who, in the discussion following upon Dr. Taylor's paper, said: "First, everyone was pretty well satisfied that pellagra had something to do with the diet; now theories are being urged in favour of a protozoal or bacterial origin of the disease. It seems to me that this is largely a psychological reaction, rather than a reaction based on reliable data. Dr. Sambon has made quite a stir in medicine on account of his free-lance methods of theorizing about different diseases. For instance, blackwater fever, which men in India feel sure is connected definitely with malaria, is attributed by Sambon to some special organism.[1] It is the same way in regard to pellagra. These theories have a psychological basis rather than one founded on actual data. So far as our position is concerned, it should be a conservative one, and we should take the ground that as far as we can tell, a corn diet has some

---

[1] It is surprising that Captain Nichols should not be able to adduce better evidence against the many facts brought first by Sir Patrick Manson, then by myself, to prove the specific nature of blackwater fever, than the statement that "men in India *feel sure* that it is connected definitely with malaria"!

definite connection with pellagra, and that in our prophylaxis we must cut out this article of diet among predisposed persons. Until further studies are made we are not justified in going into the air for any hypothetical protozoal or bacterial origin of this disease."

Conclusions.

It is quite likely that my conclusions will meet with a certain amount of scepticism. By propounding my views before making a thorough investigation in the field, I courted ridicule in the event of failure, dubitation in the event of success; but the risk of failure was small, because my facts were sound, and the analogies I relied upon appropriate. As to unbelief, sometimes it is my own attitude towards the work of others.

As regards this preliminary report, although embodying my principal data, it does not give anything like a complete account of the many facts on which my conclusions are based. I have in my notes a great mass of material which, if necessary, could be drawn on to amplify the evidence I have submitted. It will be noted that I have given chapter and verse for all the information I have derived from the literature of the subject, and that names of people who kindly gave information, as well as the names of places visited, and the names and addresses of patients referred to, are fully mentioned, so that anyone interested in the subject can, without difficulty, verify my statements.

My contention that maize, either sound or damaged, could not be the cause of pellagra, was based principally upon the striking differences existing between the distribution of the pellagra endemic stations and that of the areas of maize consumption, as well as on the irrefutable fact that true pellagra was known to occur in people who had never eaten maize. Spanish experience was overwhelming on this point.

In the course of my investigations I found that the stations of pellagra endemicity are sharply

outlined, and that they are scattered like oases in the maize-eating expanse, and I was able to prove that these endemic centres of the disease have remained exactly the same throughout centuries, just like the centres of malarial endemicity. Had pellagra been due to imported deteriorated maize, as generally believed, its topographical distribution in successive years would have exhibited a constant shifting from place to place with the necessarily irregular market distribution of the unconfiscated deteriorated grain. Moreover, I found absolutely typical cases of pellagra in both children and adults who had never eaten maize. I was able to show that pellagra was no new disease when first described by Frapolli, Odoardi, and Fanzago, but that already in the middle of the eighteenth century it was as widely distributed throughout Italy as it is now, and occupied in each region the very same stations along more or less swift-running water courses. The constant absence of pellagra in mountainous districts, where I frequently found maize, the staple food, badly deteriorated by *Penicillium glaucum* and other moulds ; the constant occurrence of the disease, year after year, in the same endemic centres notwithstanding the vigilance there exercised over the incriminated grain ; the fact that, as proved by Tebaldi, Devoto, Alpago-Novello and others, pellagrins certainly improve when fed with sound maize, all show that this cereal, whether sound or damaged, can in no way be regarded as the causative agent of pellagra.

I have shown that in Italy all measures based on the maize theory have signally failed in the struggle against pellagra, and that the alleged considerable decline in the prevalence of the disease within recent years is neither more nor less than a statistical error. Indeed, what reliance can be placed on the reports of Pellagra Commissioners who claim to have cured numberless outdoor pellagrins by means of a plateful of mid-day soup on about thirty consecutive days, when

already a century ago such men as Strambio and Cerri had conclusively proved that good food continued for several years, in patients tended under the very best conditions, fails to overcome the disease even in its earliest stages! And again, what reliance can be placed on statistical data openly admitted to be juggled with like marbles at a sleight-of-hand performance? Cerutti (1908) speaking of the influence of the measures enforced by the law of 1902 on the accuracy of recent statistics, says: "Many communes endeavoured to reduce (for economic reasons) their pellagrin lists as much as possible. There was indeed one commune of our Province which before the law of 1902 reported in round numbers 1,000 pellagrins, but after the passage of the law this number was suddenly and mysteriously reduced to only 59!" Pellagra, like malaria and other endemic diseases, has indeed its ebb and flow of prevalence and intensity, but the official statistics show a fictitious rather than the actual state of affairs.

Having demolished the maize idol, it was necessary to build up a new theory. I began by studying the endemiology of pellagra, and I found that pellagra is essentially a disease of mountain valleys. In Europe it occupies the foot-hill districts of the great southern highland region comprising the Pyrenees, Alps, Carpathians, and Balkans. I also noticed that several authors had observed its occurrence along the course of rivers and canals. Important features to my mind were the scattered distribution of its endemic centres; its double seasonal incidence; its limitation to field labourers; its absence from towns; its non-contagiousness outside the endemic centres.

Then I turned to the symptomatology and pathology of the disease, and I found that the characteristic eruption may recur for several successive years at the same seasons, viz., spring and autumn, after the patient has left the infective centre, and long after the abolition of maize from his diet; a

fact pointing to a parasitic cause, and, in any case, strongly adverse to a toxic one. Finally I endeavoured to explain the phenomena peculiar to pellagra by arguments of analogy supplied by such diseases as malaria, sleeping sickness, dengue, kala-azar, yellow fever, syphilis, Rocky Mountain fever, and other more or less allied parasitic diseases, and I came to the conclusion that pellagra also must be a parasitic disease, probably of protozoan origin, and that it must be transmitted by some kind of arthropod alternative host, probably a Simulium. The protozoan nature of the disease was suggested by the many striking analogies with other protozoan diseases, and more especially with syphilis, trypanosomiasis, and kala-azar; the Simulium carrier was suggested by the peculiar mountain-valley distribution, the association with streams, and the exceptional double seasonal incidence. I then formulated the Simulium theory of pellagra just as, in 1903, I had formulated the tsetse theory of sleeping sickness.

In Italy I was able to quite definitely establish that the pellagra stations are found irregularly scattered along certain streams of swift-running water; that the disease is practically limited to the field labourers who work in its endemic centres; that towns are absolutely immune, notwithstanding constant intercourse with numerous pellagrins from the country; that pellagra is not hereditary, as generally believed; that it is not transmitted by means of lactation; that within its stations it affects the entire population without distinction of sex or age; that children may contract the disease as early as the fourth or even the third month from birth, provided they are brought out of doors and exposed to the infective agent; that there is a definite correlation between the epidemic seasons and the age of infection in children; that the disease is not transmissible outside of its endemic centres; that the endemic centres of pellagra are at the same time the

stations of Simulium ; that the same meteorological conditions which hasten or retard the appearance of the winged or imago stage of the Simuliidæ also hasten or retard the appearance of the exanthematic recurrences of the disease ; and that overflows give rise to a great increase both in the number of sand flies and in the prevalence of pellagra. Moreover, whilst the maize hypothesis fails to explain the characteristic epidemiology of pellagra, there is not a single fact which the Simulium theory does not satisfactorily cover.

The examination of hundreds of pellagrins of all ages, and more especially the systematic examination of a large number of infants and children within the endemic stations of the disease, have convinced me that the characteristic rash is the earliest and, from the diagnostic standpoint, the most essential manifestation of pellagra. The striking periodical recurrence of the eruption at spring time and in autumn under the direct influence of solar light, point very forcibly to a parasitic organism exhibiting alternate periods of latency and activity, remaining for a time quiescent or hibernating, as it were, in some internal organ, then affecting, in its swarming periods, the regions usually bare and exposed to sunlight, probably in correlation. with the life habits of a necessary alternative host.

So far all endeavours have failed to demonstrate a parasitic agent in pellagra, but my researches have been limited to the examination of blood films. I have not had the opportunity of making a single autopsy. It is possible that the parasite may have escaped observation on account of ultra-microscopic dimensions ; indeed, we know of pathogenic organisms (peripneumonia of cattle, mosaic-disease of tobacco) so diminutive in size that we are unable to see them even with our highest powers unless they be aggregated in masses, or their presence can only be inferred from the faint opalescency to which they give rise in culture liquids, or else because they are apt to be retained by sufficiently compact filter

bougies. However, there may be other possibilities of abscondence so strikingly illustrated by such diseases as kala-azar and syphilis, or by the extraordinary difficulty of finding the macroscopic and comparatively large adults of certain filariæ, such as *Filaria recondita* in dogs presenting multitudinous larval forms of this nematode in their peripheral blood.

The demonstration of the causative organism would have been extremely interesting, but the finding of the carrier was far more important with regard to the prevention and ultimate extirpation of the disease. There are a number of diseases, such as Rocky Mountain fever, dengue, and yellow fever, of which we know the carrier, although as yet we have been unable to demonstrate the parasite either in the human or the invertebrate host. In yellow fever the discovery of the carrier alone has rendered possible the stamping-out of this deadly scourge, as has been proved by Colonel Gorgas, U.S. Army, both in Cuba and in the Panama Canal zone.

The many analogies existing between the epidemiology of pellagra and that of the best known, insect-borne diseases; the constant association of the disease with Simulium-infested streams; the absence of any other arthropod with similar distribution that might account for it; the striking correlation between the fly and the disease in wide geographical distribution, peculiar topographical exigencies, extraordinary double season of activity, and marked influence of temperature, heavy rains and inundations; are all facts which strongly point to Simulium as the necessary carrier of pellagra. And the mass of evidence is irresistible. Evidence of this kind—circumstantial evidence—is relied upon to commit human beings to the gallows, yet it hardly suffices to incriminate a fly, since we cannot be scientifically sure until we have experimental proof. In dealing with a disease like pellagra it would be

unjustifiable to lightly attempt experiments on human beings, and though I fully appreciate the great importance of experimental proof, the fact must not be overlooked that the interpretation of experiments may be just as fallacious as the interpretation of ordinary natural phenomena. Klebs and Tommasi Crudeli claimed to have produced malaria in dogs by inoculating their *Bacillus malariæ*, an organism they found in the soil of malarious localities. Sanarelli claimed to have caused yellow fever in man by inoculating his *Bacillus icteroides*, which Reed and Carroll proved to be a variety of the hog-cholera bacillus. Richardson claimed to have produced genuine rheumatism by administering or injecting lactic acid. And quite an army of pellagrologists, headed by Balardini and Lombroso, have claimed to have reproduced true pellagra both in animals and men, sometimes in themselves, by inoculating beneath the skin, injecting into the veins, or administering by way of the mouth, the special bacteria, fungi, or toxic products they had isolated !

This spring in Italy I had no opportunity to attempt any direct experiments, but at Città di Castello, in conversation with Professor Centonze, and Dr. Betti, director of the local foundling hospital, I discovered that illegitimate children, born of non-pellagrin parents, had contracted pellagra soon after being sent out to be nursed in pellagrous localities. Notwithstanding the fact that the infants were nursed by pellagrin women, and that in all probability they were occasionally given a few grains of corn papped in the nurse's mouth, as is customary amongst the peasant women, I consider these cases to be conclusive, because we know that the disease is not transmitted by pellagrin nurses when suckling away from the endemic centres, and that maize can no longer be regarded as the cause of pellagra.

The foregoing Report is reprinted from the JOURNAL OF TROPICAL MEDICINE AND HYGIENE.