

of from one to eight per cent., in combination with citric and malic acids. It is a volatile, oily fluid, soluble in water, and, when fresh, nearly odorless and tasteless. On standing it turns brown and develops the familiar odor of tobacco. The exact structure of the nicotine molecule ($C_{10}H_{14}N_2$) is not yet known with certainty. It surely contains two organic groups, one of which is pyridine. The other has been thought to be piperidine and, more recently, a hydrated pyrrol ring. Moore and Row believe that the molecule contains a reduced pyridine ring. Besides nicotine dried tobacco contains pyridine and other decomposition products and an oil which is of importance in determining the flavor.

As a medicine tobacco is obsolete. Among its former uses were the reduction of strangulated hernia and intestinal obstruction by tobacco enemata; the resuscitation of the apparently drowned by blowing smoke from a reversed pipe into the rectum; the relief of baldness and other skin diseases by its external application. Lumbermen and other ignorant persons sometimes treat wounds by the disgusting use of tobacco sputum. Though still retaining its place in the Pharmacopœia, it is too dangerous to be of practical value. Its importance depends wholly upon the prevalence of its use as a luxury.

PHYSIOLOGICAL ACTIONS.—Nicotine is classed by Schmiedeberg with pilocarpine. Its most notable effects are increased glandular activity (salivation, sweating, and lachrymation), contraction of the non-striated muscles of the alimentary tract (vomiting and catharsis), of the bladder (micturition), of the iris (myosis), and of the arteries (increase of blood pressure). These effects are due to stimulation of the sympathetic nerve ganglia. They are for the most part but temporary, stimulation giving way to paralysis. They are just the reverse of those due to atropine. But the latter acts on nerve terminations in glands or muscle cells, so that, while the effects of nicotine are prevented by the previous administration of atropine, those of atropine are uninfluenced by nicotine.

Moderate doses of nicotine cause slowing of the pulse followed by a return to normal or to a rate slightly above normal. Large doses cause no slowing at all. It must be remembered that the heart is slowed by depressor or inhibitory influences coming through the vagus and accelerated through the sympathetic. Both sets of nerve impulses must pass through ganglia before reaching the heart muscle. Nicotine at first stimulates the ganglia on the vagus, thus causing slowing of the heart, while it afterward paralyzes them and so produces the opposite effect. The action is further complicated by the fact that the accelerator ganglia are probably also affected, and still further by a direct action on the cardiac muscle fibres or the nerve terminations in them, for, after removal of the ganglia, nicotine first slows and then quickens the heart.

The blood pressure is markedly though temporarily increased by nicotine, owing to stimulation of the vasoconstrictor ganglion cells. The pressure may rise to two and a half times the normal. The subsequent fall is due to paralysis of the same ganglia. Brunton and Tunnicliffe show that pyridine causes a fall, and Moore and Row therefore attribute the rise to the reduced portion of the nicotine molecule. This effect on the blood pressure is important. Obviously its frequent repetition might produce the most widespread results—results having to do not only with the vessels themselves, but also with all the organs whose supply of blood is affected. Accordingly Huchard and others attribute to this action many of the evils resulting from the abuse of tobacco.

As to the effects on the coronary circulation, though of great clinical importance, little is known. Beyer perfused nicotinized blood through the excised mammalian heart and found a short period of increase followed by a decided and permanent decrease of the volume of the coronary circulation. This appeared to be independent of any change in the action of the heart itself. His results, however, are not altogether conclusive, and it

would be unsafe to infer that in man the use of tobacco causes such changes.

The respirations are first quickened and deepened, and hence there is the appearance of dyspnoea. Larger doses cause decreased respiratory activity and the breathing becomes progressively slower and shallower. In lethal doses it is the arrest of respiration that causes death. These results are due to stimulation of the respiratory centre in the medulla, followed by paralysis of this centre.

The stimulation and subsequent paralysis of glandular secretions by nicotine has been especially studied in the salivaries. As the nicotine acts only on the ganglion cells, when secretion has been stopped by its activity may again be brought about by the injection of muscarin or pilocarpine as these act on the nerve endings, or by mechanically stimulating the nerves between the ganglia and the gland. The same facts have been established in regard to sweating by Langley. There is no evidence that the secretion of urine is increased by nicotine, though micturition results from contraction of the bladder wall.

The contraction of the involuntary muscles of the alimentary canal is probably due to stimulation of the sympathetic ganglia in the walls of the organs. The result is the vomiting and purging, so prominent in cases of acute poisoning, and perhaps the mild catharsis which is one of the ways in which an old smoker is prone to excuse his habit.

The action on the central nervous system is first one of stimulation, as shown by the increased respiratory activity and heightened reflexes and in larger doses by convulsions. The spinal cord, and particularly the lower brain centres, are chiefly involved. The stimulation is followed by marked depression of the whole central nervous system, so that when the animal does not die in the convulsions, there are slow, shallow breathing, lost reflexes, and unconsciousness.

The actions of nicotine are rapid in onset and of brief duration. They are not cumulative. It is a matter of common observation, as well as one capable of experimental demonstration, that tolerance is easily established. In some this appears to be almost absolute, while others cannot "learn to smoke" at all.

ACUTE TOBACCO POISONING.—Mild cases of poisoning by tobacco are common among smokers who have not yet thoroughly established a tolerance, and they have occurred in others from breathing air containing the smoke. Yet in spite of the extensive use of tobacco and its extremely poisonous nature, serious cases of acute poisoning are extremely rare. Death has resulted from the internal use of infusions and decoctions, from enemata, and even from external application. Tobacco is used by ignorant persons as a household remedy and thus serious poisoning has resulted from the administration of water saturated with smoke to children. Chewers have been poisoned by swallowing tobacco juice and children from sucking old pipes. Taylor describes the case of a child of three who died as a result of blowing soap bubbles with its father's disused pipe.

The use of nicotine for suicidal purposes is rare. A few homicides are recorded, of which the most famous are those of the poet Santeul and of the Count Bocarmé. The former was killed by drinking wine with which snuff had been mixed. In the other case Bocarmé killed his brother-in-law by forcibly giving him nicotine, which he had himself prepared after several months' study of the process.

The symptoms of mild poisoning, such as occur in inexperienced smokers, are nausea, vertigo, vomiting, tremor, salivation, clammy sweating, and prostration. Severe symptoms rarely result from smoking as the terrible nausea deters the smoker from carrying his indulgence to the danger point. Where nicotine or tobacco is introduced in greater quantities there is violent purging, often with abdominal pain and involuntary micturition. Clonic convulsions are always seen in severe cases provided the person affected lives long enough.

They are followed in fatal cases by mental confusion, unconsciousness, and death from respiratory failure. The pupils are generally contracted, or at a later stage dilated. The pulse is small and weak. Where still larger doses are taken, convulsions may begin almost immediately and end in death from arrest of respiration. Enormous doses of nicotine kill almost instantaneously. The Bocarmé case was fatal in about five minutes. In other cases death may be delayed for several hours or several days.

The lethal dose of nicotine is not known. According to Witthaus it is probable that two or three drops of pure nicotine might prove fatal. An infusion of thirty grains of dried tobacco leaves has caused death.

For treatment the unabsorbed drug should be removed from the stomach or rectum with the tube. Tannin is recommended as a chemical antidote to render the nicotine insoluble, and atropine in full doses to counteract its physiological actions. Stimulants and heaters should be freely used. As death results from respiratory failure, this should be met by artificial respiration.

CHRONIC TOBACCO POISONING.—Tobacco is used as a luxury by chewing, snuffing, dipping, and smoking. In chewing the poisonous substances come into close contact with the mucous membrane, but will produce little local effect beyond the mouth. Salivation is marked, since to the action of the absorbed nicotine on the glands is added the reflex action due to irritation of the buccal mucous membranes. Snuff takers suffer particularly from local irritation of the upper respiratory passages. The effects of snuff have in certain cases been modified by the presence of lead. "Dipping" is a habit, formerly seen in the South, of taking snuff by dipping into the powder a stick, which is then rubbed on the teeth or gums.

Smoking is the commonest method of using tobacco. Its effect on the upper respiratory passages is especially marked, and is due to heat as well as to the presence of chemical irritants. The nicotine and other active principles are more or less modified by partial combustion. The composition of tobacco smoke was studied in 1872 by Vohl and Eulenbergh, who claimed that it contained no nicotine. They demonstrated a long list of substances, including a series of pyridine and picoline bases, to which they ascribed the effects usually attributed to nicotine. Since then the subject has been repeatedly investigated, chemically and physiologically, and the nicotine in the smoke has been estimated at amounts varying from nothing to fifty per cent. of that in the tobacco. Heubel, Vas, and others have proven that nicotine is present, the latter finding no other poisonous substance. For practical purposes it would appear to be of little moment whether the effects of smoke are due to nicotine or to decomposition products having essentially the same actions.

Tobacco is smoked in pipes, cigars, and cigarettes. The first mentioned method is probably the most deleterious because very strong tobacco is thus used. The black, oily juice, which collects in the stems of foul pipes, and which has been shown by Heubel to be extremely poisonous, is partly taken in when the pipe is again smoked. In cigars, on the other hand, the nicotine, which is partly evaporated and partly broken up in the burning end, is to some extent recondensed and deposited in the region near the mouth. It is then thrown away with the stub. In spite of the strong lay opinion to the contrary, it is altogether probable that, used in moderation, cigarettes are the least harmful method of smoking, though they have some dangers peculiarly their own. They are so mild that the smoker is tempted to use a large number of them and thus he constantly, though slowly, absorbs a great amount of poison. The same mildness leads to their use by minors and women, and causes the smoke to be inhaled. It is said to be especially dangerous for a pipe-smoker to use cigarettes, as he thus learns to inhale the smoke, a practice which is objectionable with the pipe. The belief that cigarette tobacco contains opium, or that the paper contains deleterious substances, has little or no foundation. Neither

has the especial prejudice against Turkish and Egyptian cigarettes.

Operatives in tobacco factories are sometimes affected by the fine particles of tobacco dust in the air. In a case of the writer's, a girl of fifteen, predisposed by bad habits, late hours, and the excessive use of tea, worked for a week as "stripper" in a small room full of tobacco dust. She vomited on the first two days and fainted four times in the week. When seen, she complained of throbbing sensations in the head, violent cardiac pain, dyspnoea, and palpitations, and presented a rapid and irregular heart and marked anemia. Such symptoms are not uncommon in beginners, but tolerance is soon acquired, permitting them to work with impunity in the dust. Dowling, studying chiefly the ocular symptoms, found that forty-five out of a hundred and fifty men working in the tobacco factories of Cincinnati showed evidences of chronic tobacco poisoning. But all of these men smoked or chewed. Apart from anemia—a common symptom among girls working in factories of any sort—there was little evidence of harmful results in women or men who did not use tobacco. Workers sometimes show conjunctivitis and irritation of the upper respiratory passages; but these effects are rare, and it does not appear that the manufacture of tobacco is especially dangerous.

Before considering the effects of the continuous use of tobacco on the various organs, it should be said that harmful results are, considering its almost universal use, rare. In most cases tobacco is not the only source of the trouble, morphine, tea, coffee, alcohol, or other injurious habits being present.

The effects of tobacco on the mouth, throat, and upper respiratory passages are due to local irritation rather than to the action of nicotine after absorption. They are more marked from smoking than from chewing. And every pipe smoker knows that mild tobacco "bites the tongue" more than strong. These facts suggest that the irritation is due rather to products of combustion than to nicotine. Catarrhal inflammation of the nasopharynx with marked hypersensitiveness of the throat is common in smokers. It may extend through the Eustachian tubes to the middle ear. It is possible that the ear may be injured in another way, viz., by the production of a neuritis of the auditory nerve similar to that seen in the eye, an action of course taking place after absorption. However, this rarely, if ever, results. Excessive chewers sometimes show inflammatory conditions of the mouth and throat and extreme discoloration of the teeth, which are sometimes worn down to a level with the gums. Snuff-takers suffer from various inflammatory conditions of the nose. Inspissated masses of snuff have formed nasal calculi. It has been said that smoking predisposes to cancer of the lip. If there is any truth in this the disease is due to local irritation.

The effects of tobacco on the alimentary system have been a subject for experimental study as well as for clinical observation. They are partly due to the swallowing of sputum containing toxic substances from the smoke or bits of tobacco from cigars held long in the mouth and chewed. The stomach may also be injured indirectly through the circulatory system. The symptoms are those of chronic gastric indigestion, hyperacidity, or flatulence. These symptoms are so common and so many excessive smokers are also excessive drinkers that the importance of tobacco as a factor is difficult to estimate. In rabbits fed for months on cabbage soaked in tobacco infusion, Adler found no gastric symptoms after the first few days, and the appetite continued unimpaired. On the other hand, it has been noticed by military writers (Korloff) that where food is lacking tobacco markedly decreases the sensation of hunger.

In Adler's experiments the liver became enlarged, and on microscopic examination showed marked proliferation of the interlobular connective tissue with new formation of bile ducts, but without any involvement of the hepatic cells. These experiments were incomplete and not altogether conclusive. Adler does not draw any comparison

between the processes observed and human cirrhosis, and indeed tobacco has never been noted as one of the causes of the latter. As a result of somewhat similar experiments Kohos found small, hard livers.

The effects on the blood have been studied experimentally by Vas on puppies. After eight weeks he noted marked anemia, the hemoglobin and red corpuscles decreasing over a half. The solid residue and the alkalinity decreased a little while the white corpuscles were decidedly augmented.

Of all the effects of chronic tobacco poisoning the most important, both from their frequency and from their severity, are those which have to do with the circulatory system. Though sometimes seen in boys, they generally result from long-continued abuse. They are said to be most frequently caused by Havana cigars. Many if not most of the cases, like the writer's patient previously referred to, are predisposed by other conditions, such as alcoholic excess, emotional strain, over-exercise, nervous disease, convalescence from acute diseases, bad habits, or indigestion. Epidemics of tobacco angina, like those described by Kleefeldt and Gélineau, may depend largely on such predisposing influences. In the latter instance a series of cases appeared on a French man-of-war, where the men, debilitated by scurvy and poor food, smoked to excess in a small close apartment.

Although the clinically observed effects of tobacco have not been fully explained, the following facts are of importance: 1. The work of the heart is increased by the vaso-motor contraction and consequent increase of the peripheral resistance, *i. e.*, the blood pressure. That this results from the administration of nicotine has been amply demonstrated by experiments. But, so far as the writer is aware, it has not been shown to result in habitual smokers from each indulgence. Such proof is all the more needed since smoke contains pyridine as well as nicotine, and the effect of the former is to reduce, and not to raise, the blood pressure. 2. Any such additional work has to be done by a heart hampered by the disturbing action of the drug on the nerve centres and muscle fibres. 3. The heart is at the same time further embarrassed by decrease of its blood supply through contraction of the coronaries. That this takes place has not been conclusively demonstrated by experiments, though the work of Beyer points in this direction, but it is accepted clinically by Huchard, Farvarger, and others.

It is probable that in far the greater number of cases the cardiac symptoms of chronic nicotine poisoning are due to functional disturbances without gross pathological lesions. Occasionally, however, after long-continued abuse, hypertrophy may result from the above-mentioned factors, especially the first. Fatty degeneration and other forms of myocarditis have been attributed to the myocardial ischemia. Huchard believes that the constantly repeated vascular contractions and rises of blood pressure may result in arteriosclerosis. Tobacco is not ordinarily considered to be one of the causes of this common condition. There is, however, just a suggestion in some recent experimental work that such may be the case. If, as Huchard believes, the sclerosis may involve the coronaries, myocarditis and true angina might result as from the same conditions due to any other cause.

The symptoms most commonly seen are those of "irritable heart." They are often associated with digestive disturbances. Palpitations are commonly complained of, with dyspnoea, ordinarily mild. Asthmatic symptoms may be present. Heart pain is common; it is usually slight and transient, but every gradation exists from the mildest to the terribly severe attacks justly described as anginal. Pallor, cold extremities, cold sweating, tremor and muscular weakness, small and feeble pulse, vertigo, headache, amnesia, psychical irritation, and even aphasia or transitory hemiplegia (spinal or cerebral anemia) are considered by Huchard to result from the contraction of the vessels of the organs involved. To say the least, many of these symptoms are extremely uncommon.

Physical examination of the heart may show absolutely nothing abnormal. Generally there is irregularity or

intermittence, which may be very marked. Rapidity is common, and is especially shown in the undue degree and permanence of the increase in pulse rate on suddenly sitting up or after slight exertion. The symptoms and signs of hypertrophy, fatty degeneration, and arteriosclerosis need not be described here, since they are at best rare and doubtful results of tobacco, and do not differ from the same conditions produced in other ways.

Attacks of heart pain, severe enough to be classed as true angina pectoris, are extremely rare. Osler states (1897) that he has seen but two cases as results of tobacco. Huchard describes three forms: (1) Functional (*angine spasmo-tabagique*), due to spasm of the coronaries. (2) Organic cases (*angine scléro-tabagique*), due to organic stenosis of the coronaries. (3) A benign form (*angine gastro-tabagique*), precipitated by gastric disorder. The first of these, though the symptoms may be very severe, almost always recovers in a fortnight after the withdrawal of tobacco; the second is always fatal; the third is the most benign of all, and disappears on withdrawal of the tobacco or curing the indigestion.

The following are among the peculiarities of the angina due to tobacco mentioned by Huchard: Vaso-motor symptoms are common—pallor, vertigo, small pulse, syncope. Other evidences of nicotine poisoning, like amblyopia, may be seen. Irregularity and rapidity of the pulse are more common than in angina due to other causes. The attacks are more apt to be slight or abortive, and are usually spontaneous.

Various effects on the central nervous system have been ascribed to tobacco. Vertigo, headache, muscular tremor, and debility are not uncommon. Tobacco as a rule favors sleep, but an unusually strong cigar may have the opposite effect. Huchard attributes all these things to ischemia of the nerve centres, as he does the rare cases of aphasia and transient hemiplegia. In the experiments of Vas, already alluded to, degenerative changes were noted in the cells of the spinal and sympathetic ganglia similar to those caused by certain other poisons. Peripheral neuritis and neuralgia are described, but it is probable that serious nervous diseases of an organic nature, such as locomotor ataxia or general paralysis, are never caused. Insanity has been attributed to tobacco and a peculiar psychosis is mentioned. Its rarity may be judged by the fact that Kraepelin says he has never seen anything of the kind. Any influence that tobacco has in this respect is probably an indirect one, due to the general physical depression, or to the marked injury of some particular organ.

The effect of tobacco on the eyes is universally recognized. An amblyopia of a specific type may certainly result from the abuse of tobacco, though alcohol is often an auxiliary factor. It is commonest in men beyond the age of thirty-five, and is said to be more common in smokers than in chewers. Dowling found some evidence of amblyopia in 45 out of 150 tobacco workers, all of whom smoked or chewed. Hirschberg found 7 cases in an ophthalmic clinic of 18,000; Galezowski, from 5 to 15 in 1,000; Landolt, 12 in 2,771. Pathologically the amblyopia is considered by some to be a retrobulbar interstitial neuritis, involving the papillo-macular bundle. Recently several investigators have attributed the cause to retinal changes taking place in the macular region, the degenerative changes in the papillo-macular bundle being secondary.

There is dimness of vision, not improved by glasses. The patient may see best at night or in a dim light. The most characteristic finding is the central scotoma for color, a condition which is almost pathognomonic of toxic amblyopia. The ability to distinguish green is usually lost first, then red, and finally blue. The scotoma may later exist for form as well as for color. The periphery of the visual field remains normal. With the ophthalmoscope the papilla is normal at first or slightly congested, then evidences of atrophy appear on the temporal side of the disc and finally become general.

Certain French writers have claimed that tobacco may cause sexual impotence, and have found experimental

evidence of degenerative processes in the testicles. Symptoms of this sort are certainly not common, and again there is difficulty in establishing the fact that tobacco is the cause.

As to the effects of tobacco on the general development, the puppies to whom Vas continuously administered nicotine lost weight very decidedly, while the rabbits, to whom Adler administered tobacco, retained perfect health for months. The statistics for one of the Yale classes is said to have shown that the men who did not use tobacco gained much more rapidly in weight, height, chest girth, and lung capacity than the moderate smokers, while the latter exceeded the excessive smokers. Thus the popular belief that tobacco "stunts the growth" appears to have some support.

In some diseased conditions the use of tobacco is undoubtedly injurious, though here, if a patient has always used tobacco, the hardship entailed by giving it up may be more deleterious than its continuance in moderation. In mental diseases Bucelli considers that its use is inadvisable, particularly in convalescents. As regards tuberculosis the views of different writers have varied from those of Melier and Ruef, who considered that tobacco was beneficial, to that of Benjamin Waterhouse, who, in 1805, thought that tobacco was the cause of the prevailing ill health of Harvard students, and especially of the increase in phthisis. Recently Stern has shown that the use of tobacco may aggravate an existing glycosuria, and even, though infrequently, cause it.

Tazzinari has subjected various pathogenic organisms to the action of cigar smoke, and shown that it very decidedly retards the development of some pathogenic bacteria, and wholly prevents that of certain others. The effect was most marked on the organisms of Asiatic cholera, typhoid, and pneumonia. Some have inferred that smoking is of value in the prophylaxis and treatment of such diseases as diphtheria.

Arguments in favor of the use of tobacco on this or similar grounds have little weight. Its great value, after all, is the pleasure and mental satisfaction it affords. That tobacco is of great service to humanity in this way there can be no doubt. Most military writers admit that it is of value to soldiers, helping to pass the time in monotonous camps and acting as a nervous sedative in times of hardship and anxiety, as well as preventing the sense of hunger when food is scarce. Socially it has objections on account of its odor and in the habit of promiscuous spitting. It need not be expensive. Used in moderation by healthy adults it will seldom do serious harm. Surely it should not be classed with alcohol and morphine, but more properly with tea and coffee. The commonest of the more serious injuries are those having to do with the heart and the eyes.

The prognosis of the functional disorders resulting from over-indulgence in tobacco is good. They usually disappear promptly on ceasing the habit. If organic changes have taken place the prognosis is more grave. Thus the general or coronary arteriosclerosis, if such a lesion does result from tobacco, will not improve. The amblyopia usually recovers completely if proper treatment is instituted early enough; but, if the habit is persisted in, a high grade of ocular deficiency may become permanent.

Treatment.—Physicians should do all in their power to prevent the excessive use of tobacco, especially by women and young persons. Moderation, or better abstinence, should be observed by persons convalescing from acute diseases, those suffering from anemia, gastric disorders, cardiac abnormalities, especially myocarditis, and other depressed states, even though they may have previously smoked with impunity. The combination of alcohol and tobacco is especially dangerous. Smokers will decrease the dangers if they will use pipes with long stems and keep them well cleaned. Notoriously strong tobacco should be avoided. The smoke should not be inhaled. Cigars should not be smoked too close to the end, nor held too long in the mouth. "Cold smoking" and chewing the ends of cigars are to be avoided. Athletes in

training should avoid tobacco. Farvarger advises smoking only after meals. This decreases the quantity of tobacco smoked, and any irritating saliva which is swallowed comes into less intimate contact with the mucous membrane of the stomach.

When any of the symptoms of chronic tobacco poisoning appear, especially if the heart, nervous system, or eyes are affected, the habit should be given up entirely. This is difficult, but there is no particular danger in sudden withdrawal as "abstinence symptoms" do not occur in the same sense as they do after sudden withdrawal of alcohol or morphine. Abstinence must be prolonged, since, when symptoms have once begun, they are prone to recur. Alcohol must also be absolutely forbidden. Other predisposing conditions should receive attention. An abundant supply of easily digested food should be given and fresh air and general tonic treatment instituted.

For drugs strychnine is of value in full doses. Iodide of potassium is also recommended for the amblyopia. Tobacco angina and the other cardiac manifestations are to be treated by rest, small doses of digitalis and other heart stimulants, iodide of potassium, nitroglycerin or inhalations of amyl nitrite as in the same conditions from other causes. *Ralph C. Larrabee.*

REFERENCES.

- Adler: Journal of Medical Research, November, 1902.
Beyer: Johns Hopkins Hospital Reports, vol. ix.
Blatin: Recherches physiologiques et cliniques sur la nicotine et le tabac, Paris, 1870.
Bragge: Bibliotheca Nicotiana, Birmingham, 1880.
Brunton and Tunnicliffe: Journal of Physiology, vol. xvii., p. 275.
Bucelli: American Journal of Insanity, January, 1897.
Cushny: Pharmacology and Therapeutics, 1899.
Dowling: Cincinnati Lancet-Clinic, 1892, vol. xxix., p. 585.
Ernst: American Anthropologist, 1889, vol. ii., p. 133.
Farvarger: Wien. med. Woch., 1887, No. 11.
Heubel: Centralbl. d. med. Wiss., 1872, No. 41.
Holden: Archives of Ophthalmology, xxviii., 125.
Huchard: Bull. Méd., Paris, 1889, iii., 643.—Maladies du Cœur, Paris, 1889.
Kerr: Twentieth Century Practice of Medicine, iii., 106.
Kissling: Zeitschr. f. analyt. Chemie, 1882, xxi., 64.
Kohos: Bull. Méd., Paris, 1897, xi., 384.
Knapp: Archives of Ophthalmology, January, 1891.
Kraepelin: Psychiatrie, 1899, vol. i., p. 50.
Lancet Com. Report: Lancet, 1888, ii., 638 and 785.
Langley: Journal of Physiology, xii., 359.
Langley and Dickenson: Journal of Physiology, xi., 272 (with bibliography).
Lloyd: Twentieth Century Practice of Medicine, iii., 431.
Love: Journ. Am. Med. Assn., March 2d, 1902.
Masoin: Bull. de l'Acad. de Méd. de Belgique, 1900, No. 8.
Moore and Row: Journ. of Physiol., xxii., 273.
Munson: Military Hygiene, 1901.
Osler: Angina Pectoris and Allied States, N. Y., 1897.
Poisson: Annales d'Hygiène, vi., 385, 1881.
Polkhorst: Ophthal. Record, July, 1900.
Schmiedeberg: Grundriss der Pharmakologie, 1902.
De Schweinitz: Morris and Olliver's System of Diseases of the Eye, 1900, vol. iv.
Sée: Maladies du Cœur, 1883.
Stern: New York Medical Record, April 27th, 1901.
Tabor: Boston Med. and Surg. Journ., vols. xxx., xxxi., xxxii., xxxiii., xxxvii., xlix., and xlv. (A series of papers on the history of tobacco, with bibliography.)
Taylor: Medical Jurisprudence, 1892.
Tazzinari: Centralbl. f. Bakteriöl. u. Parasitenkunde, iv., 449, 1888.
Vas: Arch. f. exp. Path., xxxiii., 141.
Vohl and Eulenberg: Arch. Pharm., cxlvii., Abstr. in Pharm. Journ. and Trans., 1872, 367.
Waterhouse: Cautions to Young Persons Concerning Health, Cambridge, 1805.
Wertheimer and Colas: Arch. de Physiol., iii., 341, 1891.
Wharton and Stillé: Medical Jurisprudence.
Withaus and Becker: Medical Jurisprudence, iv., 770.

TOLENAS SPRINGS.—Solano County, California. These well-known springs are located about five miles north of the town of Suisun in Solano County, adjoining the famous Tolenas onyx quarries. They are reached by rail from San Francisco or Sacramento to Suisun, and thence by stage over a good level road. The resort is 1,253 feet above the sea, and is pleasantly located. On a clear day the State Capitol, Suisun Bay and Valley, and many other points of interest are easily seen. There are nineteen springs in all at Tolenas, flowing between six hundred and seven hundred gallons per hour. The temperature of the water varies from 60° to