inseparable from it. In it the patient does not merely complain of altered sensations and feelings, but has gone a stage further and translated these into terms of definite disease, from which he is certain he is suffering, and his conduct is modified accordingly. Many patients have an idea that they may have syphilis or cancer, or ulcer of the stomach, and consult their doctor on this account. But this in itself does not constitute hypochondriasis, for after adequate examination and explanation they may be convinced that their fears are groundless. It is the person with the fixed idea, unalterable by argument, that he has some definite disease and will not therefore take food, or only certain foods, and will not touch other persons for fear of contaminating them, or will not walk lest he suddenly drops down dead from heart disease, or who spends his time constantly examining some part of his body which he considers diseased, or constantly washes and changes his linen because he thinks he is verminous—that is the true hypochondriac. It is in some cases a truly terrible affection, and is often as incurable as a case of chronic delusional insanity.

Traumatic Neuroses.

It would take too long to discuss traumatic neuroses in all their aspects, complicated and increased as they have been by the Workmen's Compensation Act, but a few words are necessary. No signs or symptoms are found in these cases differing from those mentioned in my previous remarks. The manifestations may be those of malingering, of hysteria, of neurasthenia, of hypochondriasis, or even of true melancholia. The only peculiarity is that after trauma it sometimes happens that there is a mixture of hysteria and neurasthenia with some malingering. According to legal decisions hysteria and neurasthenia (including, of course, hypochondriasis and melancholia) are psychical or physical changes and have to be compensated. But malingering, being pure fraud, gets no compensation, and the great difficulty is to prove that the case is one of pure malingering. Sometimes the doctor can discover this himself, but at other times it can only be proved by outside evidence. For instance, a man after injury may have paraplegia, not organic, as it does not conform to this, but apparently hysterical. If, however, there is evidence that when not under observation so far as the man knows he is seen to walk and run in a perfectly normal manner he is an obvious fraud.

Psychical shock producing neurasthenia may occur without physical injury. A lady in a tramcar saw a following car approaching too rapidly and thought the guard would be killed, but beyond a very slight impact of the cars nothing happened. But the lady got out of the car in a state of fright, fainted, and was afterwards at home suffering from profound neurasthenia for weeks, and was given heavy damages at the assizes.

Again, a man is in very great danger owing to an alarming accident, say, of a falling crane crushing him to death; perhaps he escapes with a bruised foot which soon recovers, but he develops neurasthenia lasting many months. And it is not uncommon for some simple injury, say, of a finger, to be followed by hysterical paralysis of sensation and motion of the same arm. In these cases, although the original slight injury soon heals, compensation must be paid so long as the neurasthenia or hysteria persists.

Finally, I would say that although after trauma the neurasthenia is due to a molecular nerve change similar to those of an ordinary acquired neurasthenia from business worry which recovers perfectly in weeks or months, yet I think that in cases of more severe injury due to falls from heights or injuries to head, and also if the accident has been a very terrifying experience (such as being whirled round a revolving shaft), it is possible for the nervous molecular changes to be so intense that recovery never occurs, in spite of full compensation having been paid. The man is "never the same as he was," and occasionally passes into melancholia and sometimes commits suicide.

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SOME APPLICATIONS OF PHYSIOLOGY TO MEDICINE.

III.—BLOOD PRESSURE AND HEART ACTION IN SLEEP AND DREAMS:

THEIR RELATION TO HAEMORRHAGES, ANGINA, AND SUDDEN DEATH.*

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THIS is an important, and in some of its aspects an almost unexplored, field of study, with an obvious bearing on many questions. Precise data on the subject are naturally somewhat difficult to obtain. The present paper contains some results of slowly accumulating observations carried on by the writer as opportunities presented themselves over a long series of years.

Changes in Normal Sleep.

The slowing of the pulse rate (noted by Galen) and the respiration during sleep has long been known to be accompanied by a lowering of bodily temperature, a great reduction in metabolic activity and heat production, depression of reflexes, diminished secretion, etc. There is general agreement as to a definite lowering of the systolic blood pressure, varying in different conditions and as recorded by different observers, but often amounting to 15 to 30 mm. Hg at the end of two hours' sleep; the pressure gradually rises in the later portion of the night's sleep. Greater reductions have been noted in persons with high pressures in the daytime. Thus some years ago Brooks and Carroll in 39 "hypertonic" subjects with an average systolic pressure of 204 mm. found a fall of 44 mm. after two hours' sleep; at the moment of waking it rose 22 mm. from the level present in sleep. More recently, in the last year or two, C. Müller in normal persons found the systolic pressure to be down to 94 mm. in men and 88 mm. in women during sleep, after a small dose of veronal. Blume, in men and women with moderate day pressures, recorded falls of 15 mm. and 21 mm. respectively, while in those with high day pressures the falls averaged 31 mm. and 39 mm. Much importance has been attached by some writers to this reduction of pressure; it has even been regarded, though on very insufficient grounds, as the determining cause of sleep.

It must be borne in mind that in the recumbent position a fall of aortic pressure would be necessary to prevent the pressure in the cerebral arteries from being higher in the horizontal than in the erect position—from the influence of gravity, the hydrostatic factor of the weight of the column of blood between the levels of the heart and the brain. Allowance for this factor in the recumbent posture cuts down the observed lowering of arterial pressure to a comparatively small amount, probably much too small to play the potent rôle that has been ascribed to it in the production of sleep. Further, the crude analogy of unconsciousness caused by an arrest or sudden great diminution in the blood supply to the brain cannot be regarded as valid when applied to the induction of the normal process of sleep.

Diminished vascularity of the brain substance during sleep has been described by various writers (Durham and others) on the ground of direct observations on exposed portions of the brain surface. A similar change has been inferred from the plethysmographic records obtained by Mosso and his followers, who found evidence of an increased volume of blood in the limbs (arm, etc.) during sleep, and assumed this to be attended by lessened vascularity of the brain, the converse conditions being present after awaking. But this hypothesis has to be revised in view of Leonard

*A communication on this subject was made to the International Physiological Congress at Edinburgh on July 26th, 1923. Part I of this series was published on January 13th, 1923 (p. 51), Part II on August 11th, 1923 (p. 215).

Hill's work establishing the practical accuracy of the old Monro-Kellie doctrine that the amount of blood within the skull is a constant quantity, whilst its distribution in arteries, capillaries, and veins respectively varies in different conditions. Weber's more recent work indicates that when there is less blood in the limbs there is more in the abdomen, not in the brain.

Plethysmographic observations have clearly shown responsiveness to stimuli during sleep, inducing alterations in the volume of a limb and showing certain changes in the distribution of the blood in the vascular system. But such observations give no information as to the state of the aortic blood pressure, upon which the pressure in the cerebral arteries depends.

Relations of the Period of Sleep to Some Diseased Conditions.

In accordance with the accepted view that the vital activities, as indicated by heart action, respiration, blood pressure, temperature, and general metabolism, reach their low-water mark in the early hours of the morning, it is easily intelligible that death from illnesses involving progressive exhaustion and a gradual running down of the machinery of life should often take place in that period. Statistics are available which bear this out. Thus Schneider (Berlin), in a total of nearly 58,000 deaths, found that deaths were most common between 4 and 7 a.m. Watson and Finlayson (Glasgow), dealing with records of nearly 14,000 deaths, fixed the highest mortality between 5 and 6 a.m.

Many phenomena of disease, aggravation of morbid conditions and symptoms in the night, can be brought into relation with the general lowering of vital activities during sleep—for example, some respiratory troubles which may in some cases be associated with the depression in respiration naturally occurring in that period, the reduced sensitivity of the respiratory centre to the normal excitation by CO₂ with the consequent modification in the state of the blood, heightening of the grade of acidosis which may be present, development of Cheyne-Stokes respiration, etc., often associated with attacks of severe dyspnoea, etc.

Incidence of Haemorrhages, Anginal Attacks, and Sudden Death in the Night.

In contrast with the associations of depressed functions during sleep as affecting some of the manifestations of disease there is another class of phenomena for which a different interpretation is required, for they obviously do not lend themselves to explanation by the lowered vital activities of nightly rest and sleep.

In connexion with the subject of haemorrhages of various kinds and their times of occurrence and mechanism, questions arise. The time incidence of many vascular ruptures is naturally accounted for by the conditions prevailing at the moment of their occurrence—rise of blood pressure and increased stress on the walls of the vessels determining rupture at the weakest part—for example, muscular effort, the influence of gravity in certain postures, abdominal straining, etc.

But why should a weakened vessel give way during the period of nocturnal rest and sleep, since a lowered blood pressure is naturally protective against rupture? Why cerebral haemorrhage should frequently occur in the night and in sleep is a question that was asked long ago by Sir Samuel Wilks and apparently never answered. In view of the lowering of blood pressure and a diminished blood flow through the brain in sleep, why should a cerebral vessel burst at that time? A similar question has to be dealt with in the case of pulmonary haemorrhage, which, as is well known, is frequently nocturnal in its incidence. The same applies to gastro-intestinal haemorrhages.

It is, of course, a matter of familiar knowledge that true anginal pain occurring in the daytime is commonly associated with exertion or excitement involving raised blood pressure and an increased call upon the heart, the pain diminishing or passing off with cessation of the muscular effort or emotional disturbance, reduction of the blood pressure by amyl nitrite, etc. But it is also well known that anginal pain sometimes seizes the patient in the quiet

of the night, awakening him from sleep. What is to be put down as determining the onset in these cases?

Again, we know that sudden death in the night is not rare, sometimes coming thus to persons who have shown little or no evidence of serious departure from the level of their ordinary health, or at least nothing to warrant the expectation of so sudden a termination. In a former paper considerations were advanced in support of the view that the usual mechanism of such deaths is to be found in fibrillation of the ventricles, occurring in a heart which has become specially susceptible as a result of defective coronary blood supply, degenerative changes, toxic influences, etc. But, granted such predisposition, what is the exciting cause that precipitates the sudden and unforeseen disaster in the night-time?

Recognition of Two Different Conditions in Sleep.

The results obtained in the present investigation lead to the conclusion that in considering the subject of sleep we have to deal with two distinct conditions, which have strikingly different associations as far as nervous, circulatory, respiratory, and other functions are concerned: (1) undisturbed or sound sleep, attended by lowering of blood pressure, heart and respiratory rates, etc., and (2) disturbed sleep, modified by reflex excitations, dreams, nightmare, etc., sometimes accompanied by extensive rises of blood pressure (hitherto not recognized), increased heart action, changes in respiration, and various reflex effects. The circulatory changes in disturbed sleep are sometimes so very pronounced that it is somewhat remarkable that they should so long have escaped observation. So far as the present writer knows, the occurrence of marked rises in blood pressure during sleep has not even been suggested—apart from the fact that no actual measurements have been recorded. No doubt paucity of opportunities and difficulties in observation have stood in the way. But the considerations as regards the occurrence of haemorrhages, etc., in the night (stated in the earlier part of this paper) give distinct indications of the probability of important blood pressure changes being present in some instances.

Disturbed Sleep.

In connexion with the circulatory and the other phenomena of disturbed sleep there are various categories with regard to the degree in which the subject is able to recall his dreams or is conscious of the disturbances after awaking.

1. There is no recollection of the disturbed sleep or dreaming condition, though the presence of such was clearly shown by observations on the sleeper—occurrence of muttering, talking, groaning, movements of the face, fingers, etc.; reflex disturbances were evidently active in pronounced degree.

2. On awaking there is a sense of the sleep having been uncomfortable and troubled, but there is no recollection of dreaming having occurred.

3. The fact of dreaming is remembered, but not the definite sequence of the dream.

4. Vivid dreams remembered in great detail.

In all the above categories cardio-vascular disturbances, etc., have been recognized in more or less marked degree. These disturbances disappear at various periods after awaking—often in a variable number of minutes.

Distribution of the Changes in Disturbed Sleep.

The incidence of the recorded disturbances upon the various systems varies widely in different instances.

The heart's action may be specially affected by the impinging of nervous impulses on the cardiac regulating centres in the medulla, etc. There may be much acceleration of the pulse with comparatively little elevation of arterial pressure; there may be a strong cardiac impulse, with or without sensations of palpitation.* On the other

* In contrast with the slowed pulse rate which is normal in the small hours of the morning, there is sometimes an acceleration at this period, apart from the development of abnormal rhythms, true tachycardias, etc., and without evidence of the more extensive disturbances of blood pressure, etc., described in this paper. Such acceleration is probably ascribable to reflex influences which have become operative during the preceding period of sleep in the earlier part of the night.

hand, the arterial tone may be mainly influenced, vasoconstriction being chiefly instrumental in causing a large rise of pressure, attended in some instances by moderate or slow heart rates; in accordance with Marey's law the high blood pressure acts by increasing the controlling influence of the vagus centre over the rate of beat. A strong cardiac impulse and a large pulse wave may be prominently in evidence. Again, both heart and arteries may be markedly influenced, giving a high blood pressure with strong and rapid cardiac beats, powerful cardiac impulse, etc.

The respiration is sometimes much altered in the way of augmentation or irregularity, but there is no constant association between these changes and the circulatory disturbances; there may be marked respiratory changes while there is little or no evidence of circulatory alteration. Long ago Hammond described notable respiratory disturbances in dreams while describing the pulse as being unaffected, except in regard to slight irregularity ascribable to the respiratory alterations. In addition to the circulation and respiration the disturbances of troubled sleep may extend, in varying degree, over other systems, somatic and visceral, as evidenced by sweating, tremors, vomiting after awaking, etc. It is obvious that such disturbances acting on various functions in different ways may be responsible for important effects in some conditions of disease.

A notable feature (remarked long ago by Hughlings Jackson) is the absence (apart from somnambulism) of large movements of the limbs, etc., even during dreams of vigorous exertion, while movements of fingers, lips, etc., may occur, contraction of distal muscles being practicable while proximal ones fail. It would seem that impulses from the cerebral cortex can sometimes reach the medullary centres (cardiac, respiratory, vasomotor, sweat, etc.) while failing to activate the large muscles of the limbs even during dreams with strong emotional content.

The Dreaming State in the Dog.

The phenomena observed in the human subject are evidently paralleled by what is recognizable in the healthy dog during dreams of hunting, etc., with the familiar movements of toes and paws, tail and ears, biting action, series of subdued barks, etc. The heart is often rapid and irregular with inhibitory pauses, bouts of acceleration, etc., while a violent cardiac impulse may be perceived; respiration is frequently hurried and irregular, with gasps, etc. The knee-jerk may be increased—as Lombard noted in man during a dream of active movement. It has not been found practicable to get actual measurements of blood pressure that are satisfactory, for disappearance of the changes present in the dreaming state is very quick when the animal awakes. But the finger on an artery has sometimes given unequivocal evidence of a rise of blood pressure.

Some Characters of the Nervous Disturbances.

The extent and intensity of the functional disturbances which may be set up during troubled sleep and the dreaming state are remarkable, though quite intelligible in view of the diminution or suspension of the control normally exercised in the waking state by higher neural mechanisms, which come to be more or less completely in abeyance during sleep; released from such control the lower mechanisms are apt to give exaggerated responses to stimuli which would have comparatively little effect in the daytime. Thus afferent impulses (somatic or visceral) which would have only slight and quite different effects in the waking state may call forth complex and pronounced reflex responses. The influence of afferent impulses in provoking and shaping the course of dreams need not be emphasized. Potent in this respect are impulses from the viscera which in the waking state would only be productive of slight sensations of discomfort—headache, nausea, etc.; in sleep elaborate responses may be set up, especially when unrestrained emotional processes are called into action with their resultant effects on both cerebro-spinal and autonomic innervation—excitation of sympathetic, etc.

Such emotional excitation is apt to reach a high grade of intensity from lack of the balance and restraint normally exercised by the fully active mechanisms of ordinary consciousness, especially by those subserving the higher levels of mental function acquired through experience after the infantile stage of life.

The suddenness of development of the functional disturbances in blood pressure, heart action, etc., in the dreaming state is an important feature. As is well known, most dreams are of very brief duration as regards the actual time occupied, a number of seconds or a very few minutes often sufficing for a dream which is subjectively a long and complicated one—for example, an apparently long and varied dream has been recorded as running its course between the beginning and the ending of a clock striking midnight. The associated functional disturbances may thus be set up with unusual abruptness, as compared with the waking state—as, for instance, in ordinary muscular exercise. It follows that there is little or no time for the coming into play of the various adjustments and compensations in the circulatory and respiratory systems, etc., that are operative in muscular exercise; in the latter the rise of arterial pressure is checked by gradual dilatation of the vessels of the skin and the working muscles, while the heart accommodates itself with the aid of increased coronary blood supply, etc. Thus the blood pressure rise in certain dreams may be both large and steep in ascent. The call on the heart, through its nervous apparatus, etc., may also be a sudden one.

Influence of the Recumbent Posture.

So far as the rupture of a weakened cerebral artery is in question the hydrostatic factor in the recumbent position is an added consideration; the weight of the column of blood between the levels of the head and the heart, which reduces the cerebral artery pressure in the standing position, is now largely out of action; with a given aortic pressure the pressure in a cerebral artery is naturally higher by a very appreciable amount (varying according to the elevation of the head) in the recumbent than in the erect posture, and the danger of a cerebral haemorrhage during a rise of aortic pressure is necessarily increased.

Observations on Blood Pressure, etc.

The subjects examined were persons mostly between the ages of 30 and 65, all, so far as was known, without organic disease of the circulatory system. The observations were made quickly after the awakening of the subject, the apparatus having been kept in readiness for immediate use. Systolic blood pressure was measured by the auditory and tactile methods, diastolic pressure by the auditory method. On occasions when no measurements could be made convincing evidence of the occurrence of extensive changes was obtained by ordinary digital examination of arteries, palpation of the cardiac impulse, etc. The following are some of the examples of the sort of observations made and the nature of the results obtained.

Subject No. 1.

The effect of walking upstairs (twenty steps) was compared in this person with the disturbances occurring in sleep. The pulse rate was raised from 80 to 90-95, the systolic from 120 to 140, and the diastolic pressure from 80 to 90; the observations were made while the ascent was being continued, not after its cessation. Ordinary walking exercise on a fairly level road caused comparatively slight changes in the heart rate and the blood pressure. In the same subject some days previously atropine (1/50 grain hypodermically) raised the pulse rate from 81-82 to 130, with systolic and diastolic pressures of 135 and 75-80 respectively, as compared with 115 and 70 before atropine. Abdominal straining (expulsive efforts) raised the systolic blood pressure only a few millimetres.

It is evident that in this individual the stress on the circulatory system was vastly greater during such disturbed sleep as is described above, than under the conditions of ordinary easy life with avoidance of sudden violent effort, emotional excitement, etc. The actual height of pressure attained during the disturbed sleep was, no doubt, decidedly higher than as measured after awaking when it is declining with some rapidity.

Hour of Observation.	Pulse Rate.	Systolic Pressure.	Diastolic Pressure.	Pulse Pressure.
1.0 a.m.	75			
7.0	62			
8.0	65	110	75	35
8.20 breakfast (in bed)				
8.50	75			
9.15	60-70	125	75	50
9.30	70	125	75	50
9.45	70	125	75	50
11.30	70	125	80	45
12 noon. Subject got up				
12.25 p.m. Sitting quietly	85			
12.55	81			
12 midnight. In bed after first sleep (somewhat disturbed)	70	140	80	60
Next morning—				
6.0 Subject awoke with feeling of disturbed sleep but no memory of definite dream. Arterial sounds (auditory method) very loud and the murmurish phase very pronounced.	62	182	105	77
Another reading two or three minutes later	—	165	95	70
6.15	60	145	90	55
6.0	58-60	115	70	45
8.0	60	130	80	50
10.20	76	120	70	50

During the day the pulse rate was generally 76 to 80.

Subject No. 2.

Subject in bed in afternoon. While asleep he had lain on the right side with the right arm pressed on by the head so that the right radial pulse was abolished. The left radial pulse was found to be very fast and the artery large and strikingly tense, immediately after awaking; these unmistakable evidences of an extensive rise of blood pressure speedily passed off. The sleeper reported having been under the influence of a pronounced nightmare, with the illusion of his lying prone near the door of a house while he heard a visitor approaching along the drive; he had vivid and distressing sensations of ineffectual efforts to rise. The nightmare was no doubt determined by the posture, the pressure on the arm, and the ischaemia caused. After awaking numbness and tingling were felt in the right hand, while the radial artery became very large and the skin flushed—evidently after-effects of the ischaemia.

Subject No. 3.

A subject, who had some symptoms of gastro-intestinal disturbance but was pursuing his usual avocations, had in the course of a night of broken sleep a dream in which he felt lively resentment at the irritating conduct of an official on a public occasion—a vivid dream but not distinctly a nightmare; there was no sense of fear, oppression, ineffectual effort, etc. On his awaking it was found that there was no sense of palpitation, no sweating, and no subjective alteration in respiratory sensations; no marked change in the respiratory movements was observed. But the cardiac impulse was greatly increased in force and felt over a larger area than usual in this person. The pulse was accelerated from a normal rate of 70-80 to 90-95. But the most notable change was a greatly raised blood pressure with an extensive pulse pressure, as shown by digital examination of the radials; the arteries were large and tense, obliteration difficult, and the range of the pressure variations at each beat palpably large. When examined fifteen minutes later these altered conditions were practically gone.

Some hours later another dream took place, the details of which were not clearly remembered. Similar phenomena, in somewhat less pronounced degree, were recognized; these virtually disappeared in a few minutes.

In one dream systolic pressure rose from 130 to over 200.

Emotion, Motor Effort, and Gastro-intestinal Disturbance.

While the most striking cardio-vascular effects are naturally present in dreams with a strong emotional content, it is to be noted that a vivid dream of active movement (cycling, for example) without sensations of night-

mare, etc., may cause a pronounced rise of blood pressure. Thus in an instance of this kind the pulse tension was greatly increased and the pulse pressure was extensive while the heart rate remained at 72-75; the elevation of blood pressure was evidently brought about mainly by vaso-constriction.

It is noteworthy that the amount of disturbance (circulatory, respiratory, etc.) associated with vivid and alarming dreams varies greatly in different individuals and even in the same individual under different conditions; the effects are sometimes remarkably slight in the case of dreams that are at other times attended by very pronounced effects of the kinds described above. There is reason to believe that the presence of some gastro-intestinal disturbance at the time may sometimes play a part in facilitating the development of the more marked effects on circulation, respiration, etc.

Dangers of the Circulatory Disturbances.

These cardio-vascular changes, involving sudden demands on the heart's power with great alterations in its rate and force and a steep and sometimes very extensive rise in blood pressure, are quite harmless in the healthy individual. Vivid dreams, involving hurrying to catch trains, etc., with failure to do so, are common in many persons and sometimes persistently recurrent—with no injurious consequences apparently. But the case is obviously very much otherwise with a damaged vascular system, life going on under conditions which afford only a narrow margin of safety. There may be a myocardium abnormal in certain functional respects, whether or not these be attended by recognizable structural alterations with or without obvious coronary lesions, giving a susceptibility to ventricular fibrillation, or, on the other hand, a defective arterial tree with localized weakenings (by miliary aneurysms, etc.) in the brain vessels, tuberculous damage in the lungs, ulcerative conditions in the gastro-intestinal tract, etc., where haemorrhage may readily be determined. In a heart susceptible to fibrillation a sudden call on the heart during muscular exertion and excitement in the waking state is often fatal; in the disturbed conditions of sleep and dreaming a similar mechanism is sometimes brought suddenly and strongly into action—diminution of vagus control and, especially under emotional stress, stimulation of the cardiac sympathetic together with a high blood pressure—conditions which favour ventricular fibrillation.

A possible discharge of adrenaline into the circulation under emotional excitation also comes into question, though the importance of such discharge or its existence has been denied by Stewart and Rogoff, in opposition to the well known work of Cannon and de la Paz. The time incidence of attacks of anginal pain may obviously be determined by similar conditions.

CONCLUSIONS.

It is clear that the foregoing facts must be taken as profoundly modifying the simple conception of night as the time of rest, and sleep as a condition in which quiescence prevails and recuperative changes go on, restoring the bodily and mental capacities which have become more or less reduced at the end of the hours of work and wakefulness—a period of repose also attended by sedative and beneficial effects on many morbid conditions. This conception, while true as regards undisturbed or sound sleep, has to be qualified by the consideration that night and sleep are occasionally the season of acute reflex and emotional disturbances which, in the peculiar conditions present, induce very pronounced effects on the circulatory system, throwing a formidable strain upon its weak points, whether these be cardiac, with susceptibility to fibrillation or anginal pain, etc., or arterial, with risk of rupture.

In this way the individual may, during the nocturnal period of assumed repose, be subjected to suddenly developed stresses, as estimated by the rise of blood pressure (even as measured after awaking when it is falling) and the evidences of increased heart action, far beyond what is involved in ordinary muscular exercise gradually initiated—for example, walking, cycling, slow ascent of stairs, straining, or mental excitement in certain degrees. Thus haemorrhages, the

onset of anginal attacks, and other disturbances in the night can be readily accounted for; also sudden death, probably due to ventricular fibrillation in most instances.

In the light of these observations it is easy to understand how in certain circumstances death may come like a thief in the night to a susceptible person living with circulatory conditions that approach the danger line, though these conditions may, in favourable circumstances and barring fresh developments, be compatible with many years of moderately active life.

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AN INVESTIGATION INTO THE EFFECTS OF THE ARSENOBENZOL TREATMENT OF SYPHILIS ON LIVER FUNCTION.

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ALTHOUGH salvarsan and its substitutes and modifications have now been in general use for a considerable number of years, syphilologists are not yet in complete agreement upon the method of using these remedies in the treatment of syphilis. Some, for example, rely entirely or principally upon salvarsan as a curative agent; others deem that it should be employed in conjunction with mercury or with the new bismuth preparations. There can be no doubt, however, as to the advantages of this drug; but it is not one to be used recklessly, and of late, since its more extensive use, and since its employment in larger doses and in a greater number of injections, certain untoward results have become familiar to those working with it. Modern methods have largely succeeded in abolishing, or at least diminishing, the immediate dangers or inconveniences, such as fever; but there still remain two important and serious consequences attributable to its administration—arsenical dermatitis and jaundice. Foulerton was among the first to call attention to the possible harmful effects of the arsenical compounds on the liver, regarding fatal cases of poisoning by the arsenobenzol compounds as essentially identical with poisoning by chloroform, ether, T.N.T., and phosphorus. In his experiments carried out with arsenical compounds in rabbits he found an interstitial hepatitis with injury to the parenchyma cells, and a nephritis in addition to the hepatitis. Many other workers have adverted to the possibility of serious toxic effects on the liver tissues, and indeed it would appear that these, with dermatitis, may now be regarded as being among the most common of the ill effects following the administration of the drug.

In considering the treatment of syphilis it has clearly to be kept in mind that cure may only be expected with any degree of confidence in the earlier stages of the disease; therefore in this early stage the powerful remedies available may be pushed to the degree of tolerance with justification. The problem presented to the dermatologist is twofold: first, he has to determine what amount of arsenical compound is required to give in the early or curable stage the best chance of cure; and, secondly, having decided this, he has further to consider whether this amount can be administered without risk of injury to the individual.

To the first part of the problem attention was paid by one of us and Kennaway in an earlier series of cases, and it was found that a series of ten injections of novarsenobenzol, amounting to 8.7 grams, satisfied the requirement in most cases—provided that treatment was subsequently continued with mercury. In view of the statements by competent observers as to the possible harm to the liver tissues from such a dosage, the present investigation was undertaken.

A series of 57 patients in different stages of disease, undergoing treatment with novarsenobenzol, was investigated, the liver functions being tested by methods to be described. The facts as ascertained by us are set out briefly in Table I. It will be noted that the examinations were carried out both during and at varying intervals after salvarsan administration. This was done in order that the harmful effects, if any, could be determined not only during the period when the arsenical compound was being administered, but also at varying periods afterwards, when delayed harmful effects might occur.

The investigator of hepatic function is confronted at the outset with certain physiological facts which make evident to him the difficulty of his task. Thus, the work of F. C. Mann has shown that four-fifths of liver substance can be removed from an animal without occasioning any apparent adverse symptoms, apart from some temporary shock inevitable where so extensive an operation has been performed. If, however, more than four-fifths of liver substance be removed, the animal develops convulsions, which may be prevented, at least for some time, by the intravenous administration of glucose solution. This fact is extremely important; it corroborates the common observation that even in cases of massive secondary carcinomatous deposit in the liver the only symptom of hepatic disturbance may be jaundice. There is evidently what may be termed an enormous "liver reserve," and this prevents any known test from being entirely satisfactory, because, unless a very large amount of liver tissue be put out of action, a single test may fail to give a positive reaction. We have attempted to overcome this difficulty by using a number of different tests.

Tests of Liver Function.

The tests that may be employed to determine liver function naturally fall into certain groups which are designed to investigate particular functions. Owing to the nature of the chemical reactions in some of the tests it is often extremely difficult to read the result accurately; we have therefore selected the following as being the most likely to give reliable results. They are those depending on biliary function and those depending on the lipase content of the blood.

The first group is concerned with the investigation of bile pigments and their precursors, urobilin and urobilinogen. We may here briefly summarize the metabolism of these substances. As is well known, the liver secretes bilirubin and biliverdin into the intestines; there these pigments meet the intestinal bacteria and are by them converted into various substances, the most important, from the point of view of the tests employed, being urobilinogen. Some of this chromogen is absorbed into the blood stream, and is then picked out by the liver cells, converted into bile pigment, and re-excreted with the bile. A very little passes out into the urine. But if there be any damage to the liver cells this property of converting urobilinogen into bile pigment is lost, and therefore urobilin accumulates in the blood and is excreted in excess in the urine. Hence it follows that any excess of urobilin in the urine points to damage of the liver cells, and the demonstration of such an excess may be accepted as evidence of liver defect. This phenomenon precedes the appearance of bile pigments in both blood and urine. The details of the tests employed to detect this substance are given later.

The tests depending on the lipase content of the blood are based upon observations by Whipple, who showed that after chloroform poisoning the lipase concentration of the serum rose, and that this increase could be prevented if the liver was "cut out" of the circulation. He suggested the estimation of blood lipase as a test of hepatic function, and this method has been used in this country in especial by Mackenzie Wallis.

The technique employed in the different tests is as follows:

Tests for Urobilin and Urobilinogen.

Ehrlich's aldehyde reaction: To 5 c.cm. of urine two drops of a 3 per cent. solution of paradimethylaminoazobenzaldehyde in 50 per cent. HCl are added. If the test be positive, the resulting mixture becomes deep red. Occasionally it is necessary to warm the solution to bring about the reaction. This test.