GENERAL FEATURES OF THE BLOOD

In the following pages I propose to treat in a very general way of such of the salient features of the blood as are likely to be referred to, or ought to be attended to in discussions on the nature and treatment of disease. A very large number of these features will in succession be necessarily discussed in detail by my brother contributors in connection with various diseases, and I must content myself with a very rapid survey of the whole field.

I begin with a remark which, though exceedingly commonplace, ought always to be distinctly borne in mind. Blood (and when we use the general phrase blood, we mean blood as it is discharged from the heart, not blood taken from any particular blood-vessel) is within very narrow limits uniform in composition and character under very varying circumstances; but that uniformity is the result of the delicate balancing of the many changes which the blood undergoes in nearly all the several parts of the body. As it flows through the capillaries of each of the tissues the blood puts on special characters, so that the blood of one vein differs, and may differ widely from the blood of another vein; but the changes thus brought about are of such a nature, and are so adjusted by a variety of influences, that the mingled blood of all the veins as it issues from the heart is under normal circumstances the same. Any marked alteration in the features of the blood flowing from the left side of the heart means something wrong in the tissue changes or some disturbance of compensatory influences.

Another general preliminary consideration deserves attention. The corpuscles are the only independent intrinsic constituents of the blood, the only idiohaemic elements. While the constituents of the plasma are continually passing through the capillary wall to and from the tissues, the corpuscles as a rule remain within the blood-stream. The red corpuscles, born in corners of the stream, in the red marrow or elsewhere, never leave it save under the most exceptional circumstances; the white corpuscles may at times wander out of it, but do not leave it to any great extent, at least save under special influences; whereas all the constituents of the plasma are continually coming and going. And while the circumstances determining the entrance and exit of the latter, whether these be activities of the tissues, or the physical conditions of the circulation, are
very largely under the dominion of the nervous system, the behaviour of
the former cannot be directly influenced by it; it is only in an indirect
way that any nervous event can affect a corpuscle of the blood.

In connection with this aspect of the blood it ought to be remem-
bered that the changes which are continually being effected in the
blood have, so to speak, two objects in view. The purpose or function of
the blood is undoubtedly to nourish the tissues, to carry to a tissue its
appropriate food, and to sweep away from it its waste matters; and the
primary object of the changes going on is to fit the blood for this pur-
pose in respect to all the tissues. But it thus nourishes the tissues by
means of the mechanism of the circulation; blood is driven in a certain way
round and round the body. That it may be properly so driven certain
physical qualities of the blood are necessary. For instance, the proper
circulation of the blood is dependent on the blood possessing a certain
viscosity; an increase or decrease of that viscosity means an interference
with the due stream; and so with other qualities of the blood. These
physical qualities are maintained by the action of the tissues; and this part
of the work of the tissues is no less important than that part by which each
tissue fits the blood for the nourishment of its brother tissues. Further,
while it is true that in the act of nourishing a tissue the essential factors
are the transit from the blood to the tissue of certain substances, and the
transit from the tissue to the blood of certain other substances, it is no
less true that the transit in each direction is dependent not only on the
presence of those particular substances in the blood and in the tissue, but
also on the presence of other substances which indirectly determine the
transit. Thus to take as an illustration an extreme case,—granted that
in any case the essential fact of the nourishment of a tissue is the transit
from the blood to the tissue of sugar, that transit will not be the same if
the sugar is offered in simple aqueous solution, as if it be presented as
part of the compound plasma of blood. Most probably, in the internal
struggle for existence, the economical result has come about that the
substances which are actually employed for the nourishment of the tissues
are, to a large extent, also used for maintaining these other qualities of
the blood. But it is also probable that such an economy is not complete.
Indeed it may be regarded as an open question whether the meaning of
the large proportion of serum-albumin in the plasma is not to be sought
for in the presence of this body in such quantity being necessary for the
adequate flow of blood through the blood-channels, and for the proper
transit of proteids other than itself and of other substances from the
blood to the tissues, rather than in the nutritive value of the substance
itself.

Again, we have evidence that the blood protects the tissues against
the action of bacteria and like organisms. In this aspect it governs the
nutrition of the tissue in a way different from either of the above.

In any case, in discussing the harm which may accrue as the result
of any change introduced into the blood, we ought to bear in mind that
the harm may be wrought in one or other of the ways to which we are
GENERAL FEATURES OF THE BLOOD

calling attention. Likening the blood to a medicament, we may say that it may fail not only through error in the quantity or quality of the active drug, but also through the vehicle or medium being unsuitable.

Bearing these considerations in mind, we may inquire what are the several changes which may take place in the blood. And we may first turn to the changes of blood as a whole.

Volume or quantity of blood.—The space supplied by the combined vascular channels contains a quantity of blood, which under ordinary circumstances is in man calculated to be equal in weight to about one-thirteenth of the whole body. This mode of stating the quantity presupposes a certain normal composition and specific gravity, as indeed does also the method of determining it; since the quantity remaining in the body after all that can be shed has been shed, is calculated upon the amount of haemoglobin retained in the body.

We have in fact no accurate observations on the volume of blood irrespective of its composition. Probably the mere volume is of no great moment. As a mere store of material it contains probably a surplus of everything, and a little less or a little more of the whole surplus cannot produce any great effect. Of more importance is the volume in relation to the total capacity of the blood-channels. But this capacity is variable, and by vaso-motor action can be so adapted to the quantity present, at least within certain limits, that the rate of flow and the pressure on the capillary walls remains, within limits, the same with varying quantities of blood. Hence, also, within limits, neither the addition nor the withdrawal of blood produces any marked change in the blood-supply to the several tissues. Neither plethora, in the old sense, nor its opposite, has any physiological significance. At the same time it must not be forgotten that an excess of blood may lead to an accumulation in the venous channels on the other side of the capillaries, and while not directly affecting the supply to the tissues, may produce physiological effects.

Reaction.—Since blood is the great agent of the chemical changes of the body, the chemical reaction of the blood as a whole assumes great importance. The chemical changes wrought by means of the blood must be influenced by the blood being alkaline, neutral, or acid; and by the amount of its alkalinity or acidity. Normal blood is alkaline, the alkalinity in man being equivalent to that of from 320 to 390 mgs. of sodium carbonate for every 100 grms. of blood. This normal condition is like the other normal conditions of the body, an equilibrium established between contending processes and hence complex in origin. The reaction actually tested is that of the plasma, but this is governed by processes taking place in the red corpuscles; for these bodies, by virtue of changes taking place in them, can give up to or take from the plasma substances whereby the alkalinity of the latter is increased or diminished. It is apparently through the action of the red corpuscles that the alkalinity of the plasma (or serum) decreases after blood is shed, and that an increase of carbonic anhydride in the blood actually increases instead of diminishing the alkalinity.
This complexity is illustrated by the experience that the alkalinity, while it may be diminished by the continued administration of acids, cannot be correspondingly increased by the continued administration of alkalies; that it is not influenced by the secretion of gastric juice, and that the diminution of alkalinity by violent exercise is less than that by moderate exercise, being moreover largely dependent on the proportion of proteid matter in the food taken at the same time. The alkalinity of the blood is part and parcel of the alkalinity of the tissues in general; it is not the consequence of the alkalies in the food being in excess of the acids, but comes about because the general metabolism of the body results in an alkaline reaction. The white corpuscles appear to have no share in the matter, but the red corpuscles, as we have just said, do seem to play a part.

Specific gravity.—Since the corpuscles are heavier than the plasma, the specific gravity of the whole blood may be affected by a mere change in the number of red corpuscles. It may, of course, also be affected by a change in the density of the plasma and corpuscles (for a change in the one would bring about a change in the other) without any change in the number of corpuscles. Or a change in the number of corpuscles and a change in the density of the plasma might occur at the same time, the change in the two factors being in the same or contrary direction. As a rule, perhaps, a low specific gravity is accompanied by a scantiness of haemoglobin due, most frequently, to a diminution in the number of red corpuscles, but sometimes to the corpuscles containing less hemoglobin.

In health the determination, by various methods, of the specific gravity of the blood has given results varying from 1050 to 1060, the more common result being about 1056. Though the blood in different veins may differ in specific gravity, the venous blood is not materially or uniformly denser than arterial blood. The blood of the pregnant female is of low, that of the fetus or new-born animal of high specific gravity. In certain diseases, especially in anaemia, and particularly in pernicious anaemia, the specific gravity may be very low; cholera and diabetes are the only diseases in which it is known to rise beyond the limit observable in health. It is worthy of notice that any obstruction to the flow along the vessels at once distinctly increases the specific gravity. Haemorrhage lowers it, but the normal or nearly the normal is very quickly regained. Dilution of the plasma by the injection of innocuous dilute fluids, normal saline fluid for instance, similarly lowers it; but the effect also soon passes off, and though by repeated injections a low specific gravity may be maintained for some time, yet a rise to the normal or nearly to the normal speedily follows the last injection. The return to the normal after dilution may be explained by the escape of water from the interior of the vessels, and this appears to take place chiefly in the splanchnic area. The interpretation of the effects of haemorrhage is not so clear. We may suppose that the lost volume of blood is in the first instance replaced by plasma only. Though we know
that hæmorrhage stimulates the production of new red corpuscles, it is
difficult to believe that these can make their appearance in sufficient
numbers to account for the regained density, seeing that this may occur
within less than half an hour. It looks as if the system got rid of the
water of the extra plasma, and regained its density by acquiring a smaller
volume.

Whatever view we take of the nature of the process of transudation
of lymph, a lowered specific gravity due to a diluted plasma must,
by the changes in the osmotic powers, influence that process, and so the
nutrition of the tissues. Hence the effect of a low specific gravity thus
caused will be different from a low specific gravity due merely to a
scantiness of red corpuscles; the latter will also have effects, but of a
different kind. In attempting, therefore, to explain any feature of
disease by reference to a low specific gravity, it becomes important to
ascertain the exact way in which the specific gravity is lowered. Further,
a change in the osmotic powers of the plasma directly affects the cor-
puscles; in this way actual destruction of the red corpuscles (hæmolysis)
may be brought about. Again, when the specific gravity of the blood is
raised by a relative increase of red corpuscles, the resulting increase of
friction, both internal friction of corpuscle with corpuscle, and friction of
the corpuscles against the vascular wall, affects the physics of the circula-
tion; such a blood is driven along with greater difficulty.

We may now turn to the particular changes of the blood either going
on continuously or taking place from time to time. These fall into two
categories: the changes effected by the several tissues on the blood as it
is passing through the capillaries, and the events which occur in the
blood-stream itself.

1. The changes effected by the tissues.—These may be subdivided into
three main groups: those effected by the advehent tissues which, through
the alimentary canal, carry material to the blood, by the excretory tissues
which remove material from the blood, and by the metabolic tissues which
change the blood as it passes through them.

To deal in detail with the normal changes so effected would be to
traverse a great part of physiology; and to deal with the abnormal ones
would be trespassing on the fields of others; with regard to the
advehent tissues it may, however, be worth while to point out some of
the more striking ways in which something wrong in their action may,
by modifying the blood, work mischief in the animal economy.

Assuming that proteids are chiefly converted into peptone and albu-
mose, but to some extent into leucin and other deproteinised bodies, that
the peptone and albumose, in the act of absorption, are converted in one
or other of the natural proteids of the plasma, and that all the digested
proteids are carried to the liver, there to undergo a secondary digestion
before they are thrown on the blood-stream, the following are some of
the errors of digestion to be borne in mind as possible causes of disease,
apart from mere excess or deficiency of normal action. The proteids

1 We may in this relation neglect the entrance of oxygen through the lungs.
may be absorbed in some form other than as peptone or albumose. The conversion of the peptone or albumose into the natural proteid of the plasma may fail or may take the wrong direction. The elements of the proteid converted into leucin and other substances may be, in excess or may be deficient. Some one or other of the digested proteids may pass into the lymph-stream instead of into the portal blood, and be thrown into the general blood-stream in an unprepared condition; the importance of this diversion is shown by the fact that when in the dog the portal blood, instead of being allowed to pass through the liver, is carried, artificially, into the inferior vena cava, proteid food has poisonous effects.

Our knowledge concerning the digestion of fats is at present very imperfect and uncertain. But assuming that all the fats pass into the lymph-stream and not into the portal blood, and are carried in the lymph-stream in the main as neutral fats (having been synthesised again by the epithelium, even if, in the very act of absorption, they have been split up into fatty acids), but partly as soaps, and that both are subjected to some unknown influences during the passage along the lymphatic tract, we may assume that the blood will not be the same if the fats should find their way into the portal blood, or if the proportion of neutral fats to soaps should be changed, or if the lymphatic tract should fail to exert its normal influence on the fats during their passage along it.

Assuming that carbohydrates are converted into maltose, and that this is chiefly absorbed as dextrose into the portal blood, but partly undergoes a further change, by fermentation, into lactic or even into butyric acid, the following are some of the errors to be borne in mind. The conversion of maltose into dextrose may fail or come short, or some sugar other than dextrose may be formed. The sugar formed, of whatever nature, may pass, not into the portal blood, but into the lymphatics, and be thrown on the general blood-stream without having passed the gauntlet of the liver; and this seems a possibility especially well worthy of notice. The proportion of carbohydrate converted into lactic or other acid may be in excess, or deficient; and abnormal acids may be formed and pass into the blood.

With regard to the excretory tissues, I will content myself with the remark that these fall into two classes in respect to the influence which they exert on the blood. On the one hand—as in the case of the kidney and urea—the act of secretion may be the simple one of picking up from the blood a substance already existing in it; variations in the activity of the excretory organ in such a case have no other effect than that of removing more or less of the substance from the blood. On the other hand, the act of secretion may be more complex and include metabolic activity; the substance excreted is formed in the excreting organ previous to its ejection; as, for instance, in the secretion (which, so far as the blood is concerned, is excretion) of pepsin or the bile acids. In such a case, in the act of secretion the antecedent metabolism may go wrong and the blood in consequence be affected.
To deal with the changes in the blood effected by the metabolic tissues would lead me through a great part of physiology and into discussions concerning the nature of many diseases. I must confine myself to one or two general reflections.

Certain tissues have what may be called an outward function, by which they affect parts other than themselves, such as a muscle in moving a limb, a secreting gland in pouring forth its secretion, and so on. In such cases the metabolism is the means of carrying out the function, and may be considered as brought about for that purpose. This is conspicuously the case in a muscle. Undoubtedly the muscle in contracting pours into the blood, either directly or indirectly through the lymph-stream, what we speak of as waste products. These waste products, like other waste products, may be capable of utilisation, but they are produced, not for that secondary purpose, but because they necessarily result from the act of contraction. Other tissues, of which the suprarenal capsule may be taken as an example, have no such outward function. They undoubtedly produce changes in the blood, but these changes serve no purpose in the organ itself. They are brought about for the sake of the blood itself; the blood so changed serves useful ends in the economy. Other tissues, again, afford a combination of these features. And, indeed, perhaps the distinction just made is after all not a valid one. Each of the tissues becomes adapted to thrive on the blood as affected by the other tissues. Hence, even admitting that the metabolism of muscle was in the first instance directed merely to give rise to contraction, and so to movement, the products of the metabolism being also in the first instance carried to other tissues merely to be prepared for excretion and excreted, it might easily arise that some turn in the muscular metabolism consistent with the efficacy of the muscle as an engine of movement was of advantage to one or other of these secondary tissues. If so, this would in the course of development become fixed and exaggerated. Hence we may be wrong in supposing that muscular metabolism is shaped solely and exclusively for the good of muscular contraction. And, indeed, we have hints that it is not. The hygienic effects of muscular exercise are manifold and far-reaching; it brings about changes in the circulation and respiration which have indirect effects on the other tissues quite apart from what is going on in the muscles themselves. Still it is difficult to resist the suspicion that the good effects are in part due to the actual metabolism of the muscle itself; whether it be that substances in the blood arising in other tissues are drawn into the complex vortex of that metabolism and made use of in an anabolic way, or whether some of the stages of the muscular katabolism, and we may well believe that these are many, cast off into the blood from the muscle subserves useful ends in other tissues. If there be any truth in this suggestion we may look to further study of the blood to explain, on the one hand, how disorders of the muscular system may arise from events in other tissues, and, on the other, how this or that tissue having no other connection with the muscles than through the blood, may suffer when, as in certain nervous
affections, so large a proportion of the muscular system is out of order that the few which are sound cannot effect what is needed.

There is, of course, one metabolic feature which stands apart from all others in being common to all the tissues: in every tissue oxidation is always taking place, oxygen being supplied by the blood, and in every tissue carbonic anhydride is a conspicuous product of the chemical changes. This is true even of the liver, whose main blood-supply has already been used for oxidation purposes and become venous. The salient features of this respiration of the tissues, as it has been called, are two. In the first place, since carbonic anhydride is only one of the several products of the oxidative metabolism, and that metabolism complex in character, the carbonic anhydride not arising from the direct oxidation of carbon, but as the last step in a chain of events, no direct proportion obtains at any moment between the oxygen absorbed and the carbonic anhydride given out; the latter may be given out in quantity by a tissue which at the time is taking in no oxygen, and may not have taken in any for some time previously. In the second place, while the physical conditions of the lungs are such that arterial blood has always the same proportion of gases, and these sufficient to cover all the respiratory needs of all the tissues under ordinary circumstances, these needs are very variable, the several tissues differing from each other, and the same tissue having different needs at different times. Hence the respiratory activity of any tissue, the amount of oxygen it takes in, and the amount of carbonic acid it gives out, are determined by the tissue itself, not by the character of the blood. The margin of the respiratory value of arterial blood is so wide that it is only under extreme circumstances, those approaching asphyxia and such as cannot long be maintained, that the character of the blood at all affects the respiratory activity of the tissues.

2. The changes taking place in the blood-stream.—We may now turn to the changes which we may speak of as changes taking place in the blood-stream itself. In attempting to deal with these, however, we come upon an important preliminary consideration. In what has gone before we have had to do with the particular changes in the blood brought about by particular tissues, that is to say, by the action of the elements of the tissues lying on the other side of the wall of the vascular channel, and exerting their influences across that wall. That the tissue produces the change may be ascertained by various experiments or observations directed to this or that tissue, such as by removal of the thyroid and the like. But the blood may and indeed does undergo changes which we cannot, as yet at least, attribute to the action of any particular tissue. For instance, the introduction of a disease or toxic agent under certain conditions leads to such changes in the blood that the serum acquires in relation to the toxic agent properties spoken of as antitoxic; these properties may have a different origin in different cases, but in some cases at least are probably due to the generation in the blood of an antitoxic substance, an antitoxin. It
may be, of course, that the antitoxin is produced by the activity of some particular tissue; future researches may show this. But there are at least two other possibilities. The whole lining of the vascular channel constitutes a tissue whose influence cannot be ignored; and the corpuscles, both red and white, constitute a floating tissue of whose influence on the plasma there can be no doubt. The former may be attributed mainly to the epithelioid layer; and in the absence of any knowledge that the activities of the cells constituting this layer differ in different parts of the system—that they are different, for instance, in the veins from what they are in the arteries, or in the large vessels from what they are in the minute vessels—we may assume that the influence is chiefly exerted in the minute vessels, where the same bulk of blood is exposed to a larger area of lining. We may probably also assume that this influence is in the active metabolic tissues more or less overridden by that of the tissue itself, and that it is most prominent in a passive tissue like the connective tissue. Such an influence cannot at present be appraised; it seems, however, obvious in the phenomena of the clotting of blood, and ought not to be ignored. In the production of antitoxins, and in respect to other changes in the blood-stream, we have to bear in mind possible actions on the one hand of the epithelioid lining, and on the other hand of the corpuscles.

We may consider first the corpuscles. These, and hence the events which they bring about, are, unlike the tissue with which we have been dealing, free from the direct influence of the nervous system. By way, as it were, of compensation, they are exquisitely sensitive to changes in the physical and chemical condition of the plasma; and the consideration of their functions largely resolves itself into a study of the manner in which they react toward such changes.

The red corpuscles.—The main function of these is, of course, to carry oxygen from the lungs to the tissues. In the lungs the hemoglobin becomes saturated or nearly saturated with oxygen; this is given up to the several tissues according to their wants, the exact amount given up at each transit differing in different tissues and in the same tissue at different times; while the amount of oxygen in arterial blood is fairly constant, that of venous blood is very variable. By adequately increasing the partial pressure of the oxygen in inspired air, not only is the hemoglobin completely saturated, but an additional quantity of oxygen of high respiratory value is carried by the plasma. Under ordinary conditions, however, all the oxygen used by the body is thus carried by the hemoglobin. Hence the quantity of hemoglobin in the blood determines the respiratory capacity, but, as we have just seen, not the respiratory activity; this is dependent on the extra-vascular elements of the tissues. This quantity is mainly dependent on the number of red corpuscles, but not wholly so. A specimen of blood having the same number of red corpuscles may contain less hemoglobin than another specimen, the difference depending not so much on the size of the corpuscles, though these may vary somewhat, as on the amount of
haemoglobin carried by the same bulk of stroma. It has been urged that different kinds of haemoglobin exist, one kind carrying per unit of weight more or less oxygen than another; but this is doubtful.

Though the haemoglobin does not carry carbonic anhydride in the same distinct way that it carries oxygen, there are reasons for thinking that the former is not, as was once supposed, carried exclusively by the plasma; the haemoglobin has some share in the matter, but the exact way in which it acts has not as yet been made clear.

The red corpuscle, however, must not be considered as simply a respiratory agent carrying oxygen and influencing the carriage of carbonic anhydride. It consists of a stroma as well as of haemoglobin; and though that stroma has lost its nucleus, and with it the power of reproduction and other vital prerogatives, it is still alive, and is still capable of influencing the plasma. The existence of such an influence, which though it may be physical, osmotic, in its nature must depend on the condition of the stroma, is shown by the fact that the entrance and exit of oxygen are accompanied by the transit from the plasma to the stroma, or vice versa, of various salts, notably sodium chloride. The action of each corpuscle in this direction is of course insignificant; but the combined action of the multitude of corpuscles must not be neglected; and in tracing out the effects of diminished numbers, or other abnormal conditions of the corpuscles, regard must be had to this and other possible actions of the stroma as well as to the respiratory activity of the haemoglobin.

Even under circumstances which are compatible with health, the number of red corpuscles in a given bulk of plasma may vary considerably. This in a great number of cases is due, not to a change in the number of corpuscles themselves, but to variations in the plasma. Nevertheless it may at times be due to the corpuscles being more or less abundant; for the mean population of red corpuscles at any one time is undoubtedly a balance between the number of old corpuscles which have disappeared and the number of new corpuscles which have appeared. Though we have no means of directly determining the average duration of life of a red corpuscle, it must be short, since the whole quantity of bilirubin secreted in the bile is supplied by the haemoglobin of red corpuscles, and the production of this must entail a large daily destruction; and though the origin of the main urinary and other pigments is at present obscure, we ought probably to conclude that an additional destruction of red corpuscles takes place in order to provide an additional quantity of hemoglobin for these. To meet this daily destruction a large daily birth must also be going on. We have evidence that in the adult this birth takes place in the abundant venous sinuses of the red marrow of bone, out of special nucleated corpuscles (erythroblasts) lodged there; but that it may also occur in the spleen or even elsewhere, at any rate under certain circumstances. Some observers, however, still maintain that the precursor of the red corpuscle is a minute spindle-shaped body, the hematoblast, not unlike a blood-platelet which, living in the blood-stream,
is developed into a red corpuscle by becoming enlarged, rounded and coloured.

It is worthy of notice that the loss of blood seems to be a most potent stimulus for the activity of this process of the production of new corpuscles, whatever be its exact nature and seat. This we may interpret as signifying that the erythroblasts in the red marrow (we are here adopting the most generally received opinion) are so influenced by the changes in the plasma contingent upon a paucity of red corpuscles—so feel these changes, we may say—as to be stirred up to reproductive activity. We cannot at present explain this more fully; it seems to be one of the many instances of that response of living matter, as a manifestation of "irritability," to chemical changes in its surroundings which is denoted by the phrase "chemiotaxis."

Probably the circumstances which determine the maintenance of the balance between destruction and birth act in this chemiotactic manner; but the details of such an action and the causes of its failure in disease are at present obscure. The technique of the determination of the number of red corpuscles and the quantity of haemoglobin will be expounded elsewhere (pp. 430 and 440), and the sources of fallacy pointed out. But we may here remark that the observations which seem to show that dwelling in a high altitude increases the number of corpuscles, and so the available stock of haemoglobin, and thus provides a respiratory compensation for the rarefied air, do not seem to have been adequately checked in view of possible fallacies. Otherwise we might conclude that the pressure of oxygen in the plasma, as determined by the quantities of oxygen held in the red corpuscles, is an important chemiotactic stimulus for the reproductive energy spoken of above.

The details of the manner in which the destruction of red corpuscles takes place are at present obscure. There is no satisfactory evidence that the disintegration of red corpuscles which may be directly observed in the spleen pulp is the chief source of bilirubin; indeed, it seems probable that this does not at all serve as such a source, the destruction being there carried on beyond the pigment stages. Some observers maintain that the free haemoglobin required for the bilirubin is obtained by a breaking up of the red corpuscles in the liver itself under the direct influence of the hepatic cells. But a number of facts, such as the presence of free granules in the plasma, render it extremely probable that the disintegration takes place in the blood-stream, and that the haemoglobin and other products are strained off by the liver and other organs. We say other products, because the stroma as well as the haemoglobin has to be got rid of; in what way this is effected and what becomes of the stroma is not at present known.

The white corpuscles.—These, though far less numerous than the red corpuscles, yet by reason of their individual activity may be regarded as exercising a more potent and a more varied influence on the general nature of the plasma, and so on the events of the body as a whole. So many facts of the life-history of the white corpuscles, such as the relation of the haemic white corpuscles, or those of the blood proper, to the coelomic
corpuscles, or those of the lymph spaces, the circumstances attending their birth and destruction, their entrance into and exit from the blood-stream, and hence their paucity or abundance either in the general blood-stream or in particular vascular regions, have to be treated in such detail elsewhere that we may confine ourselves here to very general considerations.

Further, without discussing the relations of the various kinds of white corpuscles to each other,—whether for instance they are, so to speak, distinct species, or genetic phases of one or more forms only, assuming provisionally a distinction between the hyaline forms and the granular forms, and recognising the significance of the further division of the latter into basophil and oxyphil,—that is to say, into those which have affinities for basic and those which have affinities for acid dyes, and therefore presumably for bases and acids generally—as indicative of important differences in the metabolic processes in each, but neglecting the distinction between finely and coarsely granular as of secondary importance,—we may turn to the following considerations:—

Both kinds of corpuscles, being alive, are engaged in metabolic activities, and hence both take up from the plasma as food and give up to it as waste substances in solutions; indeed, we have direct experimental evidence of this. In this way they must be constantly exerting influences over the plasma. Besides this, those which are actively amœboid may be assumed to be occupied, as occasion demands, in taking up from the plasma particles not in solution. Again, the granular corpuscle, which seems to be the seat of special metabolic activity, such as may fairly be called secretive, may be assumed to discharge, also as occasion demands, special substances bodily into the plasma. We have direct experimental evidence of both these acts in the case of corpuscles placed in artificial conditions, for instance, in a "hanging drop," and subjected to an artificial stimulus, such as the presence of a micro-organism; and we may fairly assume that a similar behaviour obtains in the blood-stream under appropriate circumstances.

The same experimental observations show us, as indeed we might a priori conclude, that in the exercise of their functions these corpuscles are exquisitely sensitive to changes in their surroundings—that is, in the plasma—especially perhaps to changes of a chemical kind; so that what is called chemotaxis plays a most important part in their life-history. By virtue of this kind of irritability they react towards changes in the plasma too minute to be ascertained by any means of physical or chemical analysis at present in our power.

Thus the white corpuscles must be considered as exerting on the plasma during their life influences the exact nature and extent of which the circumstances of the moment determine; and scanty as the white corpuscles are, these influences must be of great moment to the body, and an excess or deficiency of the white corpuscles as a whole, or of any particular kind, must affect in an important manner the qualities of the plasma, and so the welfare of the body. Relying on the experimental evidence, we may conclude that the especially amœboid hyaline corpuscles
have as their work the duty of clearing the plasma of the free particles which appear in it; it must be confessed, however, that we have not adequate evidence of their performing what might be expected to be a prominent task, namely, that of clearing the plasma of the globules and spherules of fat poured into it by the lymphatics, and, indeed the labours in the amœboid way of either these hyaline or other corpuscles are of less moment than that of discharging into the plasma (whether the act be considered a secretion or not) various substances destined to produce certain effects. This seems to be especially the task of the granular corpuscles; and, as we have seen, the work of the basophil corpuscles is probably different from that of the oxyphil, though we are perhaps not in a position at present to define the difference. In some cases the substances discharged into the plasma are, we have reason to think, of the nature of ferments; and thus we may see, in a general way, how a change in the plasma so subtle as to escape ordinary physical and chemical analysis may, by acting on these exquisitely sensitive organisms, give rise to the appearance in the plasma of an agent whose effects on the plasma, and so on the body, are out of all proportion to its weight or its bulk. The clotting of blood may be taken as an instance of this activity of the white corpuscles. Put briefly, the clotting of shed blood in vitro is due to the conversion by the agency of the body known as fibrin ferment of the substance fibrinogen present in solution in the plasma into fibrin insoluble in the plasma. The conversion is not a simple and direct one; another body or other bodies than fibrin being formed out of the fibrinogen at the same time, and the weight of fibrin formed being less than that of the fibrinogen used up. The change, moreover, is not effected at one step, a precursor of fibrin, but unlike it soluble in the plasma, being formed between it and fibrinogen. The change is further dependent on circumstances other than the mere presence of fibrinogen and ferment in a liquid medium at a suitable temperature. Thus the presence of a calcium salt is equally essential; in its absence clotting does not take place. And the presence of other substances may on the one hand hinder, and on the other hand hasten the completion of the act. As regards the nature and origin of the ferment, many observers have come to the conclusion that it is of the nature of the bodies called nucleo-proteids; and there is considerable evidence that the ferment which is absent from the blood at the moment it leaves the blood-vessels is furnished upon shedding by the white corpuscles, or by some, that is a certain kind of them, through a discharge from their bodies, which may take on the form of an explosive disintegration.

It has just been said that blood at the moment of being shed appears to contain no fibrin ferment. But the absence of clotting from blood within the lung vessels under normal circumstances cannot be due merely to the absence of fibrin ferment, since very considerable quantities of active ferment can be injected into the circulation without necessarily causing clotting. If we assume (and the assumption, though probable, is still an assumption, though the evidence that circulating blood contains
fibrinogen is strong) that clotting within the blood-vessels is, like that in 
vitro, a conversion of fibrinogen by the action of fibrin ferment, we may 
infer from this that the blood contains, or may contain, substances or 
agencies antagonistic to the action of the fibrin ferment or fibrinogen.
That such substances or agencies may be generated in the blood-stream is 
shown by the action of peptone, or rather albumose. If this substance be 
added to shed blood, it does not prevent clotting; injected into the circula-
tion it does so, not only in blood while still within the blood-vessels, 
but after it has been shed. We may conclude that the albumose, while 
circulating in the blood-stream, provokes some of the tissues so to add to 
or so to alter the blood as to give rise to a something antagonistic to 
clotting. It has been suggested that this effect is produced while the 
blood passes through the liver, it being asserted that the antagonistic 
action of the albumose is not manifested if the blood be prevented from 
passing through that organ. Even if we regard this particular view as 
not distinctly proved, the albumose effects illustrate the influence of what 
we may generally call "the tissues" on the process of clotting. Con-
versely, the presence in the blood-stream of a substance which seems to 
be a nucleo-albumose brings about extensive intra-vascular clotting, though 
the addition of it to shed blood has no such effect. The complexity of 
the reaction is illustrated by the fact that if the same substance be 
injected slowly, so that a small proportion is brought to bear on the blood 
at any one time, its action is reversed; it is antagonistic to clotting, and 
produces immunity towards its own clotting influences.

Our knowledge will not at present allow us to differentiate the several 
"tissues" in respect to this influence over clotting; but accumulated 
evidence shows that in this respect the epithelioid lining of the blood-
vessels themselves plays an important part: when the inner coat, of 
which the epithelioid lining may be regarded as the active element, is 
diseased or in an abnormal condition, intra-vascular clotting takes place at 
the spot. The mere fact that the clotting is so limited to the spot, and 
does not become general, indicates of itself that the process by which the 
clotting is brought about is a complex one. An essential factor in the 
matter seems to be an aggregation of white corpuscles; and the experi-
ence that a like aggregation takes place, not only over a diseased or 
injured inner coat, but also over an inert body, such as a needle or thread 
inserted into the blood, may be taken as indicating that the corpuscles are 
gathered together by chemiotactic influence. By a chemical touch they 
recognise the difference between the normal epithelioid cell and an altered 
one, or an element of the connective tissue underlying the epithelioid 
lining, or some quite strange body. And we may perhaps also conclude 
that the same chemiotactic stimulus which brings them together excites 
them to an unwonted metabolic activity, whereby clotting comes about. 
But beyond this difficulties arise. The fact that the clotting is limited 
to the immediate neighbourhood of the exciting cause shows that the 
general blood-stream is not affected. We may take these phenomena as 
indicating that in the general blood-stream the influences antagonistic to
GENERAL FEATURES OF THE BLOOD

clotting are prepotent, and that the action of each corpuscle is thus limited to its immediate neighbourhood. What that action exactly is we do not at present clearly know, and we need not discuss it here. It is sufficient for our present purposes that it illustrates the theme in hand—the possible influences which the white corpuscles may exert under the direction of their chemiotactic sensitiveness. It follows that these must not be left out of count in inquiries and discussions concerning the modifications produced in the blood-stream by various agencies; as, for instance, in the important problem how a toxin generates its antitoxin. That in the instance of clotting the effect is total and limited is probably a special feature having a teleological explanation; in the more ordinary cases, where the general welfare of the body has to be cared for, we might expect that the influences exerted by the corpuscles would be general too. And though in the same instance of clotting the corpuscles themselves do all the work, not calling in at all the aid of what we call the tissues, this does not preclude the view that in other actions the corpuscles may effect their purpose indirectly through some influences of the tissue excited by their action; whether it be the tissue lining the blood-vessels generally or the extra-vascular elements of one or another organ of the body.

The peculiar bodies known as blood-platelets are regarded by some as a third structural element of the blood; but it is still difficult to make any definite statements about these. On the whole, the evidence goes to show that they must be considered as existing in normal blood, but this in respect to our present theme is of secondary importance, since undoubtedly in abnormal circumstances they are present in large numbers. We are not, however, at the present moment in a position to state authoritatively what is their real nature; whether they are destructive formed elements, minute nucleusless corpuscles of a special kind, and therefore agents, or whether they are deposits, precipitations of a special kind, so far analogous to granules, and therefore products. In the absence of exact knowledge, it would not be profitable to attempt to inquire what may possibly be the exact nature or limits of the influences which they may exert.

Besides the changes which may be brought about by each corpuscle, white or red, in an area of plasma immediately surrounding itself, we must take into account changes induced by substances more generally diffused in the plasma; and which, since they are at least usually present in the plasma, we may speak of as proper to the plasma, and that quite irrespective of the causes which lead to their presence; whether, for instance, they are products of the activity of the tissues, having not more than a transitory stay in the blood, or whether they belong to the blood itself. For instance, the evidence is clear that the blood normally contains an amyloytic ferment, though the quantity or at least the energy of it seems to vary widely in different animals; and there is like evidence that a peptic and even a cryptic ferment are also present. Our knowledge of the more easily studied amyloytic
ferment is greater than that of the others; but even in regard to this we are not as yet sure whether it is a body sui generis, or whether it is merely the result of a back flow from the amylolytic pancreas and salivary glands, merely passing through the blood on its way to be got rid of. The undoubted fact that sugar (dextrose) rapidly disappears even in shed blood has led some to speak of the existence in the blood of a sugar-deestroying body or ferment, and the absence from or the excess of such a body in the blood has been appealed to in explanation of diabetic phenomena. The existence of such a body cannot at present be considered as definitely proved; but there can be little doubt that the plasma does contain a number of bodies, some of which may be of the nature of ferments, others mere chemical substances acting in a simple and more direct manner; and that variations in one direction or another of the quantity of such a body present in the plasma may exert a great influence on the economy, and, indeed, produce morbid symptoms. Bactericidal substances in the plasma afford an illustration of the newly discovered constituents we are now discussing.

Thus, when we have to consider the effects of introducing the blood of one animal into the blood-vessels of another, we have to take into account not only the general properties which may be regarded as common within limits to all animals, but special properties differing in different animals; and these may in large part depend on the presence, relative or absolute, of the bodies just spoken of. One practical value of the transfusion of blood seems to be to supply adequate oxygen by means of the haemoglobin. The mere bulk of blood, as we have urged above, is, owing to the adaptive action of the vessels, of secondary importance from a mechanical point of view, unless the loss be very great; and even great loss of blood, that which is left is probably sufficient to meet the more slowly developed needs of nutrition other than those of oxygen. Against this view may be urged the clinical experience that the injection of simple saline solution is beneficial. If this be so in cases where the loss is not too great to be compensated by vaso-constriction, the increase of the bulk by the saline must work beneficially in some other way than by restoring the mechanical conditions of the circulation. Such supply of oxygen by means of the transfused blood is of course temporary only; the foreign corpuscles soon cease to be recognised in the blood-stream; they disappear, but during their stay they have met the demands of the tissues for oxygen, until such time as an adequate supply of native corpuscles has been obtained by new formation. There are no reasons for thinking that the red corpuscles of one animal, provided that difference of size does not bring mechanical difficulties to the circulation, may not serve as oxygen-carriers to the tissues of another animal. Nor are there reasons for thinking that the substances which serve as the general basis of nutrition for the tissues of one animal—dextrose for instance, and proteids, or whatever they be—will not serve in like manner for the tissues of another animal. Differences, relative or absolute, in the salt of the plasma may render the blood of one animal unfit for another;
but probably the chief cause of the blood of one animal, for instance of
a toad, being unfit for and acting as a poison towards the tissues of
another animal, for instance of a frog, is to be sought in the presence in
the plasma of one or more of the bodies referred to above.

While the blood, then, is traversing any part of its circuit, making its
way through the capillaries of the tissue, we may recognize on the one hand
the changes which are being brought about by the tissue itself, and on the
other hand those which are being wrought in the blood itself; either by
means of the corpuscles, or by other bodies, by organisms or chemical
substances, including ferments present in the plasma. To these we ought
to add, perhaps, the influences exerted by the epithelioid lining of the
blood-vessels, influences which probably are insignificant and overridden
in the capillaries, but make themselves felt in the larger vessels, and
may be different in different parts of the vascular system—in the veins,
for instance, and in the arteries, and in different veins.

The changes effected by the tissues and those carried out by the
blood itself are not, however, independent the one of the other; they
react upon each other in many ways, and in all inquiries this should be
clearly borne in mind. Thus, granted that the white corpuscles have as
their rôle the influence which they exert on the plasma surrounding each,
the very number of these corpuscles, either in the general blood-stream or
in special parts of it, is influenced by changes in the body, in the tissues,
or in the blood itself; and a mere change in number, even if each corpuscle
maintained the same action as before, would modify the events of the
body. The number of corpuscles present in the blood-stream may be
altered, a hypoleucocytosis or a hyperleucocytosis may be brought about by
certain treatments, and whether the alteration of the population be due
to actual destruction or new growth, or to mere temporary withdrawal or
flushing, the mere fact that the population is not the same must influence
the events of the body; or again, supposing the population to remain the
same, the action of this or that tissue may so influence the corpuscles,
or a certain kind of them, as largely to modify their actions.

On the other hand, as we said above in speaking of the white
corpuscles, the action of the corpuscle is not limited to its immediate
neighbourhood. It, for instance, may discharge a substance or sub-
stances into the plasma, either by way of secretion, or in a more extreme
case by actual disruption; and this or they may provoke this or that
tissue to an altered action, and so indirectly produce a marked change
in the blood.

Such effects may be especially perhaps looked for as belonging to the
white corpuscles; but the theme on which we are dwelling may be
illustrated by the red corpuscles. The blood of an asphyxiated animal is
poisonous; that is to say, when introduced into the blood-vessels of
an animal it produces effects which must be attributed, not to a mere
deficiency of oxygen, but to the presence of unwonted substances in the
plasma. During asphyxiation the lack of adequate oxygen so modifies
the metabolism of the tissues, probably the muscular tissues in particular,
that the plasma receives from those tissues abnormal products which act as poisons. This is an extreme case, the very violence of which puts a clue in our hands; but we may safely conclude that milder circumstances produce effects which, though less in degree, are on the same lines. We may infer that a deficiency in red corpuscles, or in haemoglobin, or indeed possibly some change in the nature of the haemoglobin, though not pronounced enough to produce direct respiratory troubles, may so influence the metabolism of the tissues that the blood becomes abnormal in other respects than its mere shortcoming as a carrier of oxygen, and so produce results in the body having apparently no connection with the oxygen-supply.

Examples like the above might easily be multiplied; but enough has been said to illustrate the important view of how manifold are the agencies, actual or latent, which work upon the blood. The apparent sameness which is the blood’s salient feature is but the resultant of a multitude of actions, which in health are successfully co-ordinated to each other, but which in disease cease to fit. In attempting to track out the genesis of a malady the interweaving of these many threads of the blood’s life must always be borne in mind.

M. Foster.

THE CLINICAL EXAMINATION OF THE BLOOD

ALTHOUGH hardly appreciated at their true importance, routine examinations of the blood are capable of affording valuable assistance in the diagnosis, prognosis, and treatment of certain pathological conditions. In a certain number of diseases, among which may be mentioned leukæmia, pernicious anaemia and chlorosis, the diagnosis may be rapidly and accurately arrived at by examination of the blood alone; while, conversely, should the appearances now known to be characteristic of one or other of these diseases not be found, they can as certainly be excluded. Many other diseased conditions there are also in which, although we may not be able to evolve a diagnosis from examination of the blood alone, yet we can often obtain evidence of much value when considered in relation to the results of other diagnostic methods.

Such examinations also throw light on the progress of disease, and furnish a means of judging the results of treatment more accurately than would otherwise be possible.

Within the last few years much attention has been devoted to the simplification of the various methods employed in the examination of the blood; and concurrently, by the introduction of more perfect instruments, a notable advance has been made in the accuracy and precision of our
results. Of no less importance is it that at the present time we can carry out all the necessary details of an investigation without the expenditure of more than a few drops of blood.

While, therefore, in order to justify its title, the present article will deal only with the technique of such methods as require for their performance a minimal quantity of blood, the clinical observer may rest assured that, with due care, the ease and rapidity with which the various examinations can be carried out need involve no sacrifice of accuracy.

In systematic investigation of the blood the necessary procedure will consist of several distinct processes, as follows:—

I. Microscopic examination of—(a) the fresh blood; (b) dried and stained blood-films.
II. Estimation of the specific gravity of the blood.
III. Estimation of the colouring matter.
IV. Enumeration of the corpuscles (red and white).
V. Estimation of the alkalinity.
VI. Determination of the coagulation time.
VII. Spectroscopic examination.
VIII. Bacteriological examination by means of stained specimens and of cultivations.

As a general rule, however, it will hardly be found necessary to carry out this scheme in its entirety; although experience alone can decide to which points in any given case it is desirable that special attention should be directed.

I. Microscopic Examination of the Blood.—To obtain blood for examination.—The skin of the part selected, which may be either the finger-tip or the lobe of the ear, is first washed with soap and water, and then dried carefully with a clean cloth. Ordinarily it is not necessary to employ antiseptic solutions. The skin is punctured with a quick stab either of a lancet provided with a means of regulating the extent of protrusion of the blade, which has been specially devised for the purpose, or a bayonet-pointed surgical needle of triangular section, which is perhaps more likely to be at hand. An ordinary sewing-needle should be employed only in default of anything better, as, however sharp it may be, it is more painful to the patient in its passage through the skin, especially if it be pressed slowly in instead of being plunged with one quick motion to the required depth. To avoid possibility of ill effect the instrument should be sterilised in the flame of a spirit-lamp. This precaution is indispensable when a bacteriological examination of the blood is to be made. On no account must any pressure be employed to expedite the flow of blood; nor before pricking should a tape or string be wound round the end of the finger. Professor Sherrington and myself have shown that under such circumstances as these temporary stasis of the blood-flow through the capillaries, with the addition of the lymph derived from the surrounding tissues, are sufficient to bring about so rapid and profound an alteration in the composition of the blood—affecting as
it does the number of the corpuscles, the hæmoglobin power, and the specific gravity—as to render any conclusion based on examination of the blood thus obtained quite valueless under such circumstances. It is true that without compression of the part it is not infrequently a matter of difficulty, especially in patients suffering from certain kinds of anæmia, to obtain more than a drop or two of blood; although this difficulty may sometimes be overcome by making the puncture a little deeper. It is in such cases especially that Cabot strongly recommends puncture of the lobe of the ear, as in cases of pernicious anæmia, in which attempts to get blood from the finder had failed, he found no difficulty in getting it from the ear. He is, moreover, of opinion that the ear is decidedly less sensitive than the finger; and that there is an advantage, particularly in the case of children, in a process which the patient cannot watch. Again, in a sleeping patient the ear is usually more accessible than the finger.

A word of caution is necessary lest the patient be the subject of hæmophilia, in which case hæmorrhage, even from the tiniest wound, is apt to be profuse and difficult to stop. Hence it is always a wise precaution to make inquiry concerning former bleedings. If, on puncturing the skin, the blood-flow is fairly free, it is as well to reject the first few drops, wiping them off with a clean cloth as they exude, so that any extraneous bodies about the seat of puncture may be washed away. All blood examinations should be made at about the same hour, in order that the results obtained may be comparable one with another; and the time of examination and the hours of the meals should be recorded. This is specially desirable when enumeration of the leucocytes is in question, as allowance can then be made for digestion. But, if possible, examinations should be carried out before the first meal of the day is taken, for thus only can any approach to scientific accuracy be obtained.

Histological examination of the blood.—It will generally be advisable to examine the blood both in the fresh state and also by the staining of dried cover-glass films, which have previously been fixed in one way or another.

Examination of fresh blood.—The first point is to ensure the most perfect cleanliness of all slides and cover-glasses. Each observer prefers his own particular method, the exact details of which may be immaterial so long as thorough cleansing is secured. The use of soap and water may be sufficient for this purpose; but it is usually desirable either to boil the glasses in a strong solution of sodium carbonate, or to wash them in a mixture of potassium chromate and sulphuric acid. In either case they must receive a final wash in alcohol. To obtain a specimen of blood, a cover-glass, properly cleansed in one way or another, is held in a pair of forceps or edgewise between the thumb and first finger, and its under surface brought down into contact with a drop of blood as it oozes from the puncture. The cover-glass is then, as rapidly as possible, laid on a glass slide, when the weight of the cover-glass causes the blood to spread out under it in a film of fairly even depth. If the subsequent examination is likely to take some time, it is well to prevent
evaporation by painting round the edge of the cover-glass with vaseline or castor oil. If, moreover, the slide and cover-glass be slightly warmed before use, or if some form of warm stage be employed, alteration in the appearance of the blood will take place less rapidly than would otherwise be the case. The specimen is now to be examined under the microscope, first with a comparatively low power, and afterwards, if thought desirable, with a \( \frac{1}{4} \) oil immersion lens. Microscopical examination of a specimen of fresh blood discloses the size and shape of the red corpuscles and the fashion of rouleaux formation. Thus also the relative proportions of erythrocytes to leucocytes, and the number of blood-platelets present, can be roughly estimated, and, by the appearance of fibrin filaments, the rate of coagulation. In such a preparation the filaria sanguinis hominis, and likewise the malarial parasite, may be studied in the living state.

**Examination of fixed blood.**—For study of the finer structure of the blood corpuscles, and more particularly of the leucocytes, it is necessary to stain the blood-film which has previously been dried and fixed. In order to obtain satisfactory results special attention must be directed to the preparation of the blood-films, so as to obtain a perfectly thin and even layer of blood, the process being carried out as rapidly as possible so as to prevent the occurrence of histological changes.

Preparation of the films.—After thorough cleansing of the cover-glasses, the under surface of one of these is brought into contact with the drop of blood as it emerges from the puncture. A minimal quantity of blood having thus been taken up, the cover-glass is gently dropped upon another; after which, with the aid of fingers, or, better still, of forceps, the two cover-glasses are again separated by a lateral sliding motion of one on the other. In this way a thin and, if the process have been skilfully carried out, an even layer of blood is left on one surface of each cover-glass. These must now be left exposed to the air until the blood-films are thoroughly dry. For this purpose it is convenient to place them, face upwards, on a slip of paper, and to cover them with a watch-glass, or with one-half of a Petri dish, so as to prevent deposition of dust on the film surface during the process of drying.

Fixation of the films.—Before staining the blood-films they must be "fixed" in one way or another; otherwise the staining solutions are apt to dissolve out the haemoglobin from the red corpuscles, or even to wash the thin layer of blood from the surface of the cover-glass. The method of fixation advocated by Ehrlich is a long and tedious one, involving the heating of the films for an hour or more on a brass plate to one end of which a Bunsen flame is applied. The point at which the cover-glasses should be placed on the plate is estimated by noting within what distance drops of water, let fall on its surface from a pipette, rapidly evaporate instead of assuming the spheroidal state. Or, on the other hand, the cover-glasses may be placed in a hot-air oven, the temperature of which is maintained at about \( 120^\circ \) C. for a similar length of time.

Equally good results, however, are to be obtained, according to Hardy and Kanthack, by the far simpler and more rapid method of passing the
cover-glasses three or four times through the upper portion of a Bunsen flame, as is now ordinarily done in the manipulation of cover-glass specimens in bacteriological work. Other observers, again, fix blood-films by methods other than heating. Nikeforoff, for instance, whose method is recommended by Sherrington, advises the immersion of the specimens in a mixture of equal parts of absolute alcohol and ether for periods of from five to twenty minutes. For special purposes, such, for instance, as the demonstration of karyomitosis, fixing solutions containing bichloride of mercury, picric acid, or other reagents may be employed.

To stain the blood-films.—For the method usually employed in the investigation of the histology of the various formed elements in the blood we are indebted to Ehrlich and his pupils. He not only demonstrated, in the first place, that the protoplasm of certain leucocytes contains discrete granules, but he further determined the existence of a definite relationship between the chemical constitution and the staining capacity of these cells. Thus his method and his classification of the blood-cells are based on a scheme of the micro-chemical reactions of their granules.

According to Ehrlich, the various stains employed in histological work may be divided into two main groups: (a) acid stains; (b) basic stains,—admixtures of these in certain proportions furnishing what he has called neutral stains. The stains included in the first class are classified under the term “acid,” for the reason that although chemically they are neutral salts yet the staining principle, is the acid radicle; in other words, the stain reacts tinctorially as a free acid.

Thus ammonium picrate is an acid dye because the picric acid is obviously the staining element, the ammonium base being inert in this respect. Of the other “acid” dyes the most useful for histological purposes are eosin, aurantia, induline, and orange G.; of these the first three stain well in concentrated glycerine solutions, while the last is generally employed dissolved in water.

Again, the “basic” stains are so called for the reason that in their case it is the base and not the acid on which the action as a dye depends.

Of the basic stains one of the best known perhaps is fuchsin, which chemically is hydrochlorate of rosaniline. Here the rosaniline is the staining principle and not the hydrochloric acid. Another most useful basic stain is methylene blue, of which the alkaline preparation devised by Löffler is of special value. Other basic stains in frequent use are methyl-violet, methyl-green, and safranin. Both “acid” and “basic” stains are employed in histological work on the blood for the reason that certain of the cell granules react to acid stains only, and are therefore called “oxyphil granules”; while others, which are more readily tinged with basic dyes, are described as “basophil.” The term neutrophil is now very generally abandoned, as Hardy and Kanthack and other observers have shown that the so-called “neutral” mixtures of Ehrlich react tinctorially as acid dyes, and that the fine granules contained in the cell substance of what he has described as a “neutrophil” leucocyte are really oxyphil in their affinities. Ehrlich’s original staining method has been found some-
what cumbersome and inconvenient in use, mainly on account of the
length of time consumed in carrying out the various details of it.
Fortunately, however, standard oxyphil and basophil reactions may be
obtained by the simple and rapid modification of Ehrlich’s method intro-
duced by Hardy and Kanthack. They proceed as follows:—Thin films
of blood or lymph dried in the air and afterwards passed three times
through a Bunsen flame are floated on, a solution of 0·5 grm. eosin in
100 cub. cent. of 70 per cent alcohol for half a minute or less (acid stain).
Excess of eosin is removed by washing in distilled water. The film is
then dried by gentle pressure between sheets of blotting-paper, again
passed three or four times through the flame, and counterstained in
Löffler’s methylene blue solution (basic stain). After being again washed
and dried, the films may be mounted in Canada balsam.

A description of the histological appearances brought out by the
employment of this method and the system of classification based upon it
will be found under the heading “Leucocytes.”

Stain reactions of the blood in diabetes.—Bremer devised a modifi-
cation of Ehrlich’s method as an aid in the diagnosis of diabetes. He
found that the red corpuscles of diabetic blood could not be stained with
eosin as in normal blood; although, nevertheless, they reacted to the various
so-called acid dyes. He therefore employed a special eosin-methylene
blue stain, by the use of which the red corpuscles of normal blood are
stained violet, of diabetic blood a greenish colour.

Lépine, however, has shown that this reaction is not absolutely
characteristic of diabetes, since he has obtained it also with leukaemic
blood. Bremer, partly for this reason and partly because his original
eosin-methylene blue stain was difficult to prepare, has, more recently,
altered and simplified the method considerably. The blood-film, after
drying in the air, is exposed to a temperature of about 135° C. for from
six to ten minutes; accuracy at this stage of the procedure is of special
importance, as unless the temperature exceed 129° C. the test becomes
untrustworthy. The slides, together with control slides made from normal
blood, are next stained for about a couple of minutes in a 1 per cent
watery solution of Congo red, or in Biebrich scarlet, or with the ordinary
Ehrlich-Biondi stain. The specimens are then rapidly washed and dried.

With Congo red diabetic blood is usually not stained at all, while
non-diabetic blood is coloured red; with Biebrich’s scarlet an opposite
effect is obtained, the diabetic corpuscles are stained, the normal ones
are not.

Whether these different reactions are due to the presence of sugar in
the blood, to an alteration in alkalinity, or to some other cause, is as yet
undetermined.

The red corpuscles or erythrocytes.—Under normal circumstances
the red corpuscles have the form of biconcave discs of a fairly uniform
diameter of about $\frac{3}{4}$ th of an inch. When seen under the microscope
in a single layer they are of a yellowish red colour and are non-nucleated.
In a film of moderate thickness, shortly after removal of the blood, the
corpuscles exhibit the physical peculiarity of running into small aggregations or rouleaux, so called from the supposed resemblance to a heap of coins.

In many forms of disease, particularly in wasting diseases, and in pernicious anaemia more especially, not only are the form and consistence of the red corpuscles liable to considerable alteration, but a marked diminution in their numbers is usually obvious on examination.

The number of red corpuscles normally present in the blood has been estimated by Vierordt at 5,000,000 to the cubic millimetre in man, and about 10 per cent less in woman. In the condition known as oligocythaemia, however, the number of corpuscles in the blood may become greatly decreased, sinking as low as one million per cubic millimetre; or, in severe cases of pernicious anaemia, even to half a million and under. The number of corpuscles is also diminished in leukaemia, and to a less degree usually in chlorosis and such cachexies as phthisis and the various forms of malignant disease. The number falls also, temporarily, after severe haemorrhages, whether due to traumatism or to disease, as, for instance, after the intestinal bleeding of enteric fever. Should oligocythaemia be present in high degree, this will usually be apparent in the abnormally pale colour of the blood, and the obviously lessened number of corpuscles in fresh microscopic preparations. When the diminution in the number of corpuscles is less, the employment of more accurate methods will be necessary; and in any case trustworthy information as to the actual condition present can only be obtained by enumeration of the corpuscles by means of special instruments devised for this purpose. Under certain circumstances the size of the corpuscles may undergo considerable change, the diameter sometimes becoming increased to as much as double the normal length (from 7.5 μ to 10 μ or even 15 μ). This condition, namely macrocythaemia, is apt to occur to a certain extent in any case of severe anaemia, but more especially in that form known as "pernicious." It must be carefully distinguished from the swelling of the red corpuscles which is prone to occur in hydæmic blood.

By microcythaemia, on the other hand, is understood a diminution in the diameter of the red corpuscles. These smaller bodies, or microcytes as they are called, are often globular in form, and of a more intense colour than normal. They are commonly present in pernicious anaemia, and occur in most other forms of anaemia, especially when severe; also in certain toxic conditions and infectious diseases, and after extensive burns and large haemorrhages. At present, however, but little is known of their significance, and consequently no information of importance in diagnosis is to be derived from their discovery. Some observers are of opinion that they occur as the result of degeneration of the normal red corpuscles. Gram and Graber, indeed, go so far as to regard these microcytes as the result of changes in the blood after death.

Occasionally the red corpuscles undergo marked variations in shape, becoming pyriform, spindle-shaped, reniform, cup-like, or knobbed. A certain proportion of them, however, retain their normal form. This con-
dition, named poikilocytosis—which is believed to be due in some measure to a lessened consistence in the struma of the corpuscles—has been noticed in leukæmia and in anaemic states, more particularly in pernicious anaemia. Such remarkable variations in the shape of the corpuscles have indeed been regarded by some authors as pathognomonic of the latter disease. As is well known, crenation of the red corpuscles, giving rise to the so-called mulberry and thorn-apple forms, may occur as the result of evaporation in normal blood at a varying interval after its withdrawal from the circulation; but a little experience will prevent any likelihood of confusion with the change under consideration. Nucleated red corpuscles are found not infrequently in the blood in pernicious anaemia, and in leukæmia of the myelogenic kind, and again after extensive hemorrhages. They may vary considerably in size, the presence of the larger variety (megaloblasts) being considered to be of especially grave significance.

The white corpuscles or leucocytes.—Leucocytosis.—Comparatively little was known of the differential characteristics and properties of the white corpuscles of the blood, or leucocytes as they are now more generally named, until the introduction by Ehrlich of special staining methods, by means of which the various forms of leucocytes can readily be distinguished one from another. The work of Hardy and Kanthack, and also of Professor Sherrington, in this country has added largely to our knowledge of the subject; and these observers, by simplifying the methods originally devised by Ehrlich, have rendered them more readily available for clinical research.

At the present day the name “leucocyte” has a somewhat wider significance than that of a mere synonym for the different forms of the white corpuscles which, under normal circumstances, can be demonstrated in the blood. The name as now employed includes also wandering cells, which may be found in the lymph-stream, in the serous cavities, and in the intercellular interstices of the tissues. Consequently leucocytes may be classified as—(a) tissue, and (β) haem.

The cells belonging to each of these classes are subdivided, again, according to their reaction to certain staining reagents, thus:—

(a) Oxyphil
   { coarsely granular.
     { finely granular.

(b) Basophil
   { coarsely granular.
     { finely granular.

(c) Hyaline
    { large.
    { small.

The classification of leucocytes as tissue or haemic leucocytes respectively, although convenient, is by no means definite. Dr. Gulland states that when the blood is first formed in the embryo, for a time it contains no leucocytes whatever, so that none of the leucocytes are aborigines of the blood; the coarsely granular basophil cell is found in the tissues alone, while the finely granular oxyphil cell is rarely met with elsewhere than in the blood: but, on the other hand, certain cells,
which at one period of their life-history must be looked upon as tissue leucocytes, may later be discharged into the blood-stream.

Of the haemic leucocytes the finely granular oxyphil variety is by far the most common normally, since it constitutes about 75 per cent of all the leucocytes present in the blood. The cell has an average diameter of 10 μ, and is vigorously amœboid. Its name is derived from the fact that the cell substance contains numbers of fine granules, which refract light to a slightly greater degree than the ground substance in which they lie. This cell can also be distinguished from other leucocytes by the irregular and multipartite nucleus, which usually appears to consist of a number of separate lobes linked together by fine chromatin threads. After death the various nuclear segments take on a more regular distribution in the cell-protoplasm, forming rosette-like masses; but, when living, the shape of the nucleus is constantly undergoing variation, for which reason it is generally described as "polymorphic." Opinions differ as to the cause of this diversity of shape of the nucleus, but, as has been shown by Professor Sherrington and others, it is most probably to be attributed to distortions produced by the extreme amœboid activity of the cell body. This cell is markedly phagocytic; but, as Professor Halliburton and Dr. Brodie have shown, it is readily killed and broken up by contact with solutions of certain nucleo-albumins. Vacuoles, probably containing fluid, are often to be seen in the protoplasm of the cell.

The finely granular oxyphil leucocyte corresponds to that named "neutrophil" by Ehrlich and his pupils; Hardy and Kanthack having shown that the former name is the more correct, since the granules, especially under certain conditions, obviously react to acid dyes. This leucocyte appears capable of undergoing multiplication in the blood-stream; but it is somewhat doubtful whether such multiplication takes place more commonly by karyomitosis, or by direct division of the cell.

The coarsely granular oxyphil cell differs from the finely granular variety, not only, as its name implies, in the larger size of the contained granules, but also in the larger size of the cell itself; the average diameter being about 12 μ. When examined on the warm stage it is found to be amœboid, but it contains no vacuoles, and is never phagocytic. The horse-shoe-like or reniform nucleus is fairly regular in shape. The granules contained in the cell substance are comparatively few in number and of large size. This is specially noticeable in certain of the lower animals. The granules are highly refractive, and have a marked affinity for "acid" dyes, by means of which they can be readily stained. As they colour deeply when treated with osmic acid, the granules might be regarded as fatty in nature, but they are not soluble in alcohol or ether.

The coarsely granular leucocyte has a fairly wide distribution in the various fluids and tissues of the body; but in the blood itself it does not usually constitute more than about 2 per cent of all the leucocytes present. It is, however, of special interest since, although it is not phagocytic, it apparently has certain functions of a secretory nature. Thus Hardy and
Kanthack have shown that the injection of a culture of anthrax into the blood of an animal causes a rapid disappearance of the granules in the cell protoplasm, and that such disappearance seems to be accompanied by and related to the secretion of a substance possessed of germicidal properties. Another special point of interest is that the granules of the coarsely granular leucocyte contain appreciable amounts of iron and phosphorus. It is not improbable, therefore, that, although themselves quite colourless, they are related to the hemoglobin of the red corpuscles, which latter they also resemble in their proteid nature, marked refraction, and strong affinity for "acid" dyes. In this connection, also, it is of interest to note that the coarsely granular cell is to be found in specially large numbers in bone-marrow.

The basophil leucocyte, both of the finely granular and the coarsely granular variety, requires but brief mention, as under normal conditions the first form is rarely, the second never found in the blood. The finely granular leucocyte is occasionally met with for an undetermined period after the beginning of digestion, and apparently under certain pathological conditions, for Grünbaum has found it in excess in the blood of uremic patients. This cell is of small size, spherical, and in its cell protoplasm contains numerous minute granules, which are deeply stained by methylene blue. The nucleus is irregular in shape. A sub-variety of the coarsely granular leucocyte—the "mast-zellen" of Ehrlich—in which the cell body is filled with large granules, which are stained of an intense violet-purple by methylene blue, has been found by Professor Sherrington in the blood of patients dying in the reaction stage of Asiatic cholera; and by myself in some cases of leukæmia.

The small hyaline leucocyte, or lymphocyte as it is frequently called, from the fact of its presence in large numbers in lymphoid tissue in all parts of the body, is about the size of a red corpuscle of the blood. It consists of a minimal quantity of protoplasm free from obvious granulation, in which is embedded a large spherical nucleus readily stained by methylene blue or other dyes.

The lymphocyte, numbers of which are continuously being shed into the blood by the thoracic duct, is apparently an immature form of cell. It is not amœboid. The number in the blood undergoes phasic variation, reaching its highest point between two and three hours after digestion has begun. The average number in the blood ranges between 10 and 20 per cent of all haëmic lymphocytes. This proportion, however, may be greatly exceeded in the form of disease known as "lymphatic leukæmia," in which the lymphatic glands undergo enlargement.

The large hyaline leucocyte, or myelocyte as it is also named, possesses a larger amount of protoplasm than the smaller variety. The nucleus is usually spherical or reniform, and fairly regular in outline. As it possesses a comparatively small amount of chromatin, it does not stain well with aniline dyes. The cell has not been proved to be amœboid, but nevertheless seems capable of acting as a phagocyte. In the blood it is less numerous than the lymphocyte, forming usually less than 10 per cent of the

VOL. V
haemic leucocytes. Increase in the number of lymphocytes is usually accompanied by increase in the total number of myelocytes also; this being specially noticeable in the leucocytosis which accompanies the anæmia of pregnancy, and that which ensues on typhoid fever. In lymphatic leukæmia, however, enormously as the number of lymphocytes in the blood may be increased, no such increase in that of the myelocytes has been observed. During life the cell protoplasm is apparently homogeneous, but, when dead, staining by means of methylene blue shows it to be full of exceedingly fine granules embedded in a matrix which does not take up the stain.

Leucocytosis may be most simply defined as a condition in which the number of leucocytes in the peripheral circulation is above the normal standard. It is practically impossible, however, to lay down any exact rule concerning the numbers of the white corpuscles or the excess which should be held to constitute leucocytosis. In the same normal individual variations occur at different times, and different individuals exhibit considerable range in the numbers of leucocytes in a similar volume of blood, according in some measure to the physical development and habit of life of each of them. Taking these factors into consideration, we shall not err to any great extent if we look upon the normal range in the adult as extending between a minimum of 6000 and a maximum of 10,000 leucocytes in a cubic millimetre of blood. Any number of leucocytes below the arbitrary limit of 6000 will constitute a hypoleucocytosis, or leucopenia as the condition is also named; while an excess above 10,000 would constitute leucocytosis. The ratio of white corpuscles to red is of itself of comparatively little importance, since conditions which cause an increase, for instance, in the number of white corpuscles may bring about concurrently an increase in the red.

It is, therefore, the absolute number of leucocytes in a cubic millimetre of blood which must be determined in each case. It is of no less importance, however, to determine the relative numbers of each kind of leucocyte present, as by such differential enumeration it becomes possible to discriminate the particular form of leucocytosis with which we have to deal in any given instance.

Leucocytosis may be either physiological or pathological. These two kinds may be distinguished by the fact that in the former the increase affects all varieties of leucocytes, with the exception of the coarsely granular oxyphil cell; while in the latter it is, for the most part, the finely granular oxyphil cell which is present in excessive numbers.

Physiological leucocytosis has been found in newly-born infants, in the later stages of pregnancy, more particularly in primiparse, and during the process of digestion. Massage, as Dr. Weir Mitchell has shown, is found in many instances to induce moderate leucocytosis, and so likewise does the temporary application of cold in the form of bath.

Leucocytosis in the new-born is probably to be explained by inspissation.

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1 Leukæmia, or leucocythaemia, which would be included under this definition, is treated of elsewhere. See Dr. Muir's article later in this volume.
of the blood in conjunction with more or less continuous digestion leucocytosis. Rieder and other observers have shown that hyaline cells, particularly lymphocytes, are more abundant in the blood of the newborn than are the other varieties of leucocytes. There is also a definite increase in the number of coarsely granular cells. The actual number of white cells present is considerably greater than in the adult, ranging as it does from 15,000 to 30,000 per cubic millimetre. The number rapidly declines, however, during the first two years of life, until at the end of such period the adult normal has probably been reached.

The leucocytosis of pregnancy has no clinical significance; and, since it is not present in the early stages, it is also valueless from the diagnostic point of view. Again, it is by no means of invariable occurrence, especially in multiparae; while it is liable to occur also in cases of spurious pregnancy.

Digestion leucocytosis usually occurs in healthy persons, and comes on at a somewhat variable period after ingestion of food; beginning generally about one hour after food, increasing in amount for the next two or three hours, and afterwards gradually disappearing again in three or four hours more. In a few instances the blood of persons apparently healthy shows little or no digestion leucocytosis; this, in some cases at any rate, seems to be dependent upon chronic constipation, as Von Limbeck has shown. The effect of proteid food is especially remarkable in bringing about digestion leucocytosis; a mixed dietary is followed by a less striking result, while a vegetarian diet apparently exerts no appreciable influence. The increase in the number of leucocytes following the ingestion of a meal rich in proteids may amount to as much as 30 per cent, or even slightly more. It should be remembered, however, that the actual number present will depend on the standard normal to the particular individual during the passive phase of his digestive functions. It is always advisable, therefore, to make a control reckoning of the number of leucocytes in the early morning before the patient has broken his fast.

Starvation in man, especially when of considerable duration, has been found by Luciani and Von Limbeck to result in a notable diminution in the total number of leucocytes. Prof. Sherrington, who has studied this subject in the lower animals, finds that while this is so, yet at the same time, contrary to what obtains during the opposite phase of digestion leucocytosis, abstention from food leads to a decided increase in the numbers of the coarsely granular cell.

Diseases, especially those of malignant nature, which lead to difficulty either in ingestion or digestion of food—among which may be mentioned carcinoma of oesophagus or stomach—tend eventually to bring about not only disappearance of digestion leucocytosis, but an actual leucopenia.

Pathological leucocytoses.—For descriptive purposes these may be classified under the following heads:—(i.) Inflammatory leucocytosis; (ii.) Toxic leucocytosis; (iii.) Leucocytosis of certain infectious diseases; (iv.) Leucocytosis of cachexia and malignant disease; (v.) Post-haemorrhagic leucocytosis.
(i.) *Inflammatory leucocytosis*, resulting from simple traumatism without bacterial infection, has recently been the subject of careful investigation by Prof. Sherrington. In his observations he was able to distinguish three definite stages of the process:—(a) A leucopenic phase, or hypoleucocytosis, during which the total number of haemic leucocytes falls; (b) A stage of hyperleucocytosis; (c) A second but inconstant stage of leucopenia.

The preliminary stage of hypoleucocytosis affects all the different kinds of leucocytes, but perhaps the finely granular variety more especially. This diminution holds not only for a unit volume of blood, but also relatively for the number of chromocytes, and this in spite of coincident apoplasia or inspissation of the blood.

In the second stage, that of reaction, a hyperleucocytosis occurs in which both the finely granular and hyaline leucocytes are concerned. Although this is the case there is a continued fall in the numbers of the coarsely granular variety. Finally, after a variable interval, the leucocytosis passes away, and may be succeeded by a fall which, on occasion, may again reduce the number of leucocytes below the normal average.

(ii.) *Toxic leucocytosis.*—Under this heading may be considered the results of subcutaneous, intravenous or intraperitoneal injection of various toxic substances, whether employed therapeutically or not. It has long been known that extracts, protein or dead cultures of bacteria, filtered yeast-cultures, organic substances such as fibrin ferment, hemi-albumose, peptones, nuclein, and leech extract, as also curare, tuberculin, pyocyanin, uric acid, and urates, have the effect, on injection, of bringing about a marked and rapid diminution in the number of the leucocytes. This stage of hypoleucocytosis, leucopenia, or leucolysis, as it was named by Löwit in accordance with the hypothesis advanced by him that leucocytes undergo actual destruction, is in turn followed by a hyperleucocytosis of greater or less degree, provided that the dose of toxic material received into the system be not sufficient to cause death. That the preliminary leucopenia is not due to a leucolysis has been proved by Goldscheider and Jacob, who have demonstrated that the leucocytes vanish from the peripheral circulation in consequence of their having become stored in the capillaries of the lungs. This process probably occurs in the liver and spleen also. During the second stage these leucocytes find their way once more into the general circulation, together, as certain observers believe, with others of more recent origin.

(iii.) *Leucocytosis of certain infections.*—In many of the acute infectious disorders leucocytosis has been found, more particularly in small-pox, scarlet fever, diphtheria, pneumonia, acute rheumatism, anthrax, erysipelas; and perhaps in measles. Leucocytosis has also been described in typhoid fever; but most observers are now of the opinion that it does not occur in the absence of complications. Leucocytosis is not apparent in tuberculosis or in influenza. The same has been said of malaria, but Dr. Billings has put on record a series of observations which tend to show that definite stages of leucopenia and leucocytosis undoubtedly present
themselves in the course of this disease; although these variations, being of slight extent, have been overlooked by other observers. In pneumonia, on the other hand, the process is generally so well marked as to afford most valuable aid in the diagnosis and prognosis of the disease.

The increase in the number of leucocytes is due to increase of the finely granular oxyphil variety; it begins with the rise of the temperature, and, except in cases of extreme gravity, not only continues but increases up to the crisis, at which stage a well-marked leucocytosis is a very favourable sign. On the other hand, if leucocytosis be absent or ill marked, the case will probably end in death. In scarlet fever and other diseases, in the course of which leucocytosis is ordinarily demonstrable, we can in like manner judge in great measure of the severity and the probable termination of any given case by the extent of the leucocytosis. This being so, it is obviously desirable that the blood should be more generally examined in infectious disease than has hitherto been customary. The importance of these observations is confirmed by the work of Everard, Demoor, and Massart, who state, as the result of the inoculation of guinea-pigs with varying doses of pathogenetic organisms, that while the primary result is invariably a fall in the number of leucocytes in the blood, this in turn is succeeded by a leucocytosis in those instances in which the animal eventually recovers. They add that, in immunised animals, a leucocytosis appears immediately, no stage of leucopenia being obvious.

Septic infections, whether due to streptococci or staphylococci, are usually associated with a definite leucocytosis, the number of leucocytes being often increased as much as fourfold. Such diseases as erysipelas, cellulitis, and puerperal septicæmia come into this category, and also suppurative inflammations or abscesses in any part of the body.

That the presence of collections of pus may be diagnosed from the occurrence of leucocytosis is a fact of much clinical value. Thus Stengel has found, as the result of examination of the blood in a number of cases of appendicitis, that in those in which suppuration had supervened, in consequence of the presence of the staphylococcus albus, the number of leucocytes varied from 15,000 to 40,000; while in the non-suppurative cases leucocytosis was extremely moderate or absent.

Von Limbeck has indeed asserted that leucocytosis only appears when exudation into the tissues occurs, and that the extent of leucocytosis which accompanies it is directly dependent on the degree of cellular richness of the exudate. Thus leucocytosis is a usual concomitant of inflammations of serous membranes, whether of the peritoneum, pleura, or meninges. The extent of leucocytosis, however, often bears no relation to the amount of the exudation; and in tuberculous inflammations of serous membranes leucocytosis is invariably absent, unless in the case of secondary septic infection.

(iv.) Leucocytosis of cachexia and malignant diseases.—During the course of many cachectic diseases a leucocytosis of considerable extent is apt to arise. Stengel finds that this is particularly the case in congenital syphilis and rickets, the increase in the number of leucocytes being some-
times so great as to simulate leukæmia. In such cases the diagnosis is
the more difficult as the increase in numbers mainly concerns the hyaline
leucocytes.

In the moribund a "terminal" leucocytosis is frequently observed,
especially in the subjects of protracted chronic disease. This is merely
an exaggeration of the leucocytosis of cachexia. According to Cabot and
others, this condition is specially apt to supervene in fatal cases of
pernicious anaemia. The explanation of the condition is by no means
simple; but it has been suggested that a terminal infection or a fetadation
of the circulation, with fall of blood-pressure, may bring about a
discharge of leucocytes into the circulation.

The leucocytosis of malignant disease is believed by some authors to be
due to the cachexia of the later stages. Others look upon the inflamma-
tion surrounding the focus of disease as the immediate cause. Leuco-
cytosis is more pronounced in sarcoma than in carcinoma, and tends to be
more marked the less circumscribed the growth.

(v.) Post-hæmorrhagic leucocytosis.—Loss of blood, especially if serious in
amount, is rapidly followed by a leucocytosis, the extent of which is more
or less dependent on that of the hæmorrhage on which it ensues. It may
appear within an hour or so, and may persist for several days.

Observers differ somewhat as to the exact nature of the leucocytosis;
some assert that the finely granular oxyphil (adult) cells are increased
both absolutely and relatively, others that the most noticeable feature is
an excess of the mononuclear hyaline corpuscles, and more particularly of
the lymphocytes. It is not improbable, however, that these apparently
divergent results may have relation to the cause of the hæmorrhage,
whether traumatic or pathological, in each particular instance.

Concerning the actual causation of leucocytosis much difference of
opinion exists. The current hypothesis is that the process mainly depends
on what is named "chemotaxis." Thanks in large measure to the
researches of Schulz, Von Limbeck, and of Goldscheider and Jacob
abroad, together with those of Sherrington, and Hardy and Kantack in
this country, much light has recently been shed on the processes concerned
in leucocytosis.

The mass of experimental evidence that has accumulated as the result
of the labours of various workers in this field all tends to support the
chemotactic hypothesis of leucocytosis, according to which leucocytosis
must be regarded as in the main a phenomenon dependent on a chemical
stimulus of a more or less intensive character, which is enabled to act on the
hæmic leucocytes, and also on the blood-forming organs, through the
medium of the circulating blood.

As previously stated, the injection of bacteria, or their metabolic
products, whether toxins or proteins, or even simple traumatism, brings
about, in the first instance, a rapid disappearance of leucocytes from the
peripheral circulation.

This phase was thought by Löwit to be due to an actual destruction
of corpuscles, to which process, therefore, he applied the name leucolysis.
This view is now no longer tenable since, as Schulz first indicated, the more or less complete disappearance of leucocytes from the peripheral circulation is due to an altered distribution; the leucopenia or hypoleucocytosis being coincident with a storage of leucocytes in the internal organs. That such is the case has been definitely proved by Goldscheider and Jacob, who found that the leucocytes accumulate chiefly in the capillaries of the lungs and liver.

This stage of hypoleucocytosis is due, as it appears, to a repellent action on the circulating leucocytes, and is in turn followed by a hyperleucocytosis or increase in the white corpuscles, provided that the injury inflicted on the organism be not of so severe a character as to render recovery improbable. This hyperleucocytosis may be due, as Schulz has suggested, to a secondary change in the distribution of the leucocytes, which, having been just previously packed away in the capillaries of certain of the viscera, now once again find their way back into the peripheral circulation, together with others which for the time are carried along with them, the increase in numbers above the normal being thus accounted for. The researches of Goldscheider and Jacob, however, afford reason to believe that this explanation is insufficient to account for the facts, and that at this stage the total number of leucocytes in the blood may be positively increased, although the place of origin of such additional supply may be difficult to determine.

Goldscheider and Jacob were able, indeed, to demonstrate that during this stage of hyperleucocytosis not only is the number of leucocytes in the capillary area of the pulmonary circulation equal to that of the leucopenic phase, but may be actually greater than before. It would seem fairly certain, therefore, that under the influence of chemotactic attraction the blood-forming organs are excited to greater activity, the result of which is seen in an abnormal output of cells which may happen to be stored at the time in these areas, together with simultaneous multiplication of leucocytes.

From experimental evidence we learn that the extent of the repellent action exerted on the hæmic leucocytes, as well as that of the subsequent leucocytosis, are determined, in large measure at any rate, by the virulence and the amount of the particular material injected. Thus the more potent the influence on the organism generally, the more pronounced will be not only the preliminary leucopenia, but also the secondary leucocytosis. It must be understood, however, that this statement only holds good up to a certain point; for when the dose and virulence of the noxious agent are sufficiently intense, and the consequent depression is so profound that the system is unable to rally, leucocytosis does not occur. It is possible, therefore, in most cases, to judge from the presence or absence of leucocytosis whether in any particular instance recovery will or will not take place—a sign which, as I have stated, has already been found of great assistance in the prognosis of specific infections in man.

In certain instances leucocytosis arises without any preliminary
leucopenic phase. This occurrence has been described by Goldscheider and Jacob as a result of the experimental injection of a glycerine extract of spleen; and the same has been noted in animals which are either naturally or artificially immune.

II. Estimation of the specific gravity of the blood.—Until recently records of the specific gravity of the blood in disease have been very scanty, as it was necessary to remove a considerable quantity of blood for the purpose; moreover, the operation, involving as it usually did the use of the specific gravity bottle, was by no means an easy one. Moreover, by this method it was practically impossible, except with very elaborate precautions, to take the specific gravity of uncoagulated blood; hence defibrinated blood was used on the assumption that its specific gravity does not appreciably differ from that of the fluid circulating in the living vessels.

The ingenious method devised by the late Professor Roy, however, affords a means of making rapid and accurate observations at the expense of a single drop or even a fraction of a drop of blood.

Roy’s method consists in observing whether a drop of the blood, rapidly withdrawn from the circulation and placed in a solution of known specific gravity, rises, sinks, or remains stationary in this solution.

Certain modifications of detail have been suggested by Dr. Lloyd Jones, and by myself, which have rendered it more easily applicable to clinical requirements.

The requisite apparatus consists of —

1. A series of solutions of various specific gravity, ranging from 1025 to 1070, one member of the series corresponding to each unit of the third place of decimals. For ordinary use, however, a much less number will suffice, as the numbers at the ends of the scale are seldom if ever required. In any case, however, for an extended series of observations, a considerable quantity of fluid corresponding to each degree employed should be provided. Roy originally used water to which glycerine was added in each case until the mixture was of the necessary specific gravity; but such solutions are apt to be untrustworthy, as the specific gravity is not constant, particularly if, as is often the case, a mould develop on the surface of the fluid. Fluids more suitable for the purpose may be made up from a stock solution of equal parts of glycerine and distilled water saturated with Barff’s boro-glyceride and magnesium sulphate, with the addition of a small quantity of corrosive sublimate. If the specific gravity is to be lowered, this stock solution is diluted with water, and its density can be increased to any needful extent by the addition of more glycerine and boro-glyceride. Solutions thus made have a constant specific gravity. Moreover, blood does not clot very rapidly in them. The accuracy of the graduation should be ensured in the first instance by testing the specific gravity of the fluids with an accurate hydrometer, and by controlling these results with the balance. Small quantities of these fluids should be kept in a series of two-ounce bottles, the stoppers of which have been care-
fully greased so as to prevent any change of density by evaporation. The small bottles are best fitted into wooden stands for convenience of transit.

2. A number of glass pots about 1½ inch deep and half an inch wide, of which probably at least half a dozen will be required for one observation.

3. Fine capillary pipettes, formed by drawing out a piece of small glass tubing; the last quarter of an inch should be bent at right angles to the stem. To the opposite and wider extremity a piece of india-rubber tubing should be fixed, to which the mouth may be applied when the contents of the pipette are to be expelled.

It is usually possible, with practice, to make a fairly accurate guess at the specific gravity of the blood in each case, so that six or more of the small pots may be filled from the small bottles (by means of a fairly large pipette) with fluids of the densities likely to be required. Otherwise in a first observation every alternate number may be omitted so as to have a longer range at hand. A finger is then cleaned, and a fairly large drop of blood obtained by puncture with the precautions already laid down (p. 409). The drop is drawn by suction into one of the capillary pipettes, and, the pipette being lowered at once beneath the surface of the fluid in one of the small pots, some of the blood is gently blown into it. If the pipette be held so that the end is horizontal, the drop of blood expelled, if of the same density as the fluid contained in the pot, will have no tendency either to rise or to fall; if its specific gravity be higher than that of the fluid it will tend to fall, if lower to rise. With a little care it is comparatively easy to find the fluid in which it remains stationary, or at any rate to hit upon two adjoining numbers, in one of which it may slowly rise, and in the other slowly fall. To obtain a reading correct to a decimal part of a degree we shall carefully mix measured quantities of the two numbers between which the specific gravity has previously been found to lie, and in this manner readings to one-half or one-third of a degree, or even to one-tenth of a degree, may be obtained. It is worthy of note that the portion of the blood last expelled from the pipette is not infrequently some 0.0005 above that of the portion first expelled. This difference is due partly to capillary action in filling, and partly to friction of the blood against the wall of the pipette. If extreme accuracy be desired, the difficulty can be overcome by using the corresponding portion of each drop withdrawn.

In order to avoid any trace of admixture of two successive drops of blood, and to avoid the rapid clotting which goes on in the drop received into a pipette in which blood has previously been received, a fresh pipette, recently drawn in the blow-pipe flame, should be used for each observation. It is also necessary to see that the pipettes are carefully dried, as during their cooling moisture tends to condense in them.

Method of Hammerschlag.—This, which is essentially a modification of that originally devised by Roy, differs from the latter in that mixtures of chloroform and benzol are employed instead of more or less dilute glycerine solutions.

The supposed advantage of Hammerschlag’s method is that a drop of
blood when introduced into such a mixture as that devised by him does
not tend to mix with it, but retains the appearance of a red bead.

Estimations are made in one of two ways: (a) A number of small
pots are prepared, containing a series of mixtures of chloroform and
benzol previously made up, and ranging in specific gravity from about
1035 to 1060. Into several of them in turn a drop of blood is intro-
duced, by means of a bent capillary tube, until that mixture is found in
which the drop of blood neither rises nor falls. (β) Chloroform and
benzol are mixed in an ordinary urinometer glass in such propor-
tions that, when tested by means of a urinometer possessing a somewhat
extended scale of graduations, the specific gravity of the resulting mixture
is found to be about that of normal blood (1055-1069). A drop of blood
is then blown out into the mixture at a point beneath the surface by
means of a bent capillary tube. If the bead tend to sink, chloroform is
added drop by drop; if, on the contrary, the bead tend to rise, benzol is
added in like manner. After every such addition the whole contents of
the urinometer glass should be thoroughly stirred by means of a glass
rod in order to ensure the uniformity of the specific gravity of the whole
mixture. As soon as the drop of blood no longer shows any tendency
either to rise or fall, the specific gravity of the surrounding liquid is
obviously equal to that of the blood itself. All that now remains to be
done is to take the specific gravity of the chloroform and benzol mixture
by means of the urinometer, and the result thus obtained furnishes the
required specific gravity of the specimen of blood.

Hawcroft's method.—Two mixtures of benzyl chloride (sp. gr. 1100)
and toluol (sp. gr. 0870·6) are made, the one (A) having a specific gravity
of 1070, and the other (B) having a specific gravity of 1020. With
a cubic centimetre pipette, graduated to \(\frac{1}{12}\)th c.c., one c.c. of A is
measured off into a glass tube, and the drop of blood to be tested is
then allowed also to flow into the tube. The drop of blood, having
a different surface tension, does not mix with the solution, but floats
on its surface as a tiny red globule. The graduated pipette is now
filled with solution B, which is allowed to run slowly into the mixing
tube, the tube being shaken after each addition. As B flows in, the
specific gravity of the mixture falls, and after each addition and shaking
the red globule returns more and more slowly to the surface. At last it
tends neither to rise nor sink, and, the specific gravity of the mixture being
now that of the blood itself, this can readily be calculated or read off
from the table attached to the apparatus\(^1\) sent out by the maker.\(^1\) Sup-
pose 0·5 c.c. of B to have been added, the total weight of the fluid
divided by its volume will give the specific gravity of the mixture:—

\[
\begin{array}{ccc}
1 \text{ c.c. at sp. gr. } 1070 & 1070 \\
5 & 1020 & 510 \\
6 & 10580 & 1058 \\
\end{array}
\]

\(^1\) Made by Mr. Fraser, Lothian Street, Edinburgh.
As the mixtures of benzyl chloride and toluol expand with heat they will vary in their specific gravity, so that, if exactitude be required, a correction for temperature must be made. The solutions A and B are prepared at the temperature of 15° centigrade, or 60° F., and if the temperature of the room be also 60° F. no correction will be needed. If, however, the surrounding temperature be higher than 60° F. the specific gravity of the fluids will be lowered, the fall of specific gravity being, roughly, at the rate of one degree for every 2° F.*

In his original paper Haycraft warns those who may employ his method that it is well not to allow the fumes of benzyl chloride to get into the eyes, as, the vapour being very irritating, somewhat painful smarting may result.

Method of Schmaltz.—Mention must be made of this method because, although somewhat tedious, it gives very accurate results, and a large amount of work has been carried out by its means. As, however, it involves the use of delicate chemical balances it is hardly likely to come into general use in clinical work. The blood, of which the specific gravity is to be determined, is carefully weighed in a small capillary tube (pycnometer) of known weight. By subtraction the weight of the blood is obtained, and if this be divided by the weight of an equal amount of water the specific gravity of the blood is obtained.

Whatever the method, it is, of course, only the specific gravity of the blood, as a whole, which is thus determined. To what particular factor or factors, in each instance, alterations in the specific gravity of the blood are to be attributed remains to some extent a matter of conjecture. It is obvious that the alteration may be due to one or more of the following causes:—

1. An increase or diminution in the number of corpuscles in a given volume; the specific gravity of individual corpuscles, and of the plasma remaining unchanged.

2. An increase or diminution in the density of the plasma; the specific gravity and the number of corpuscles remaining unaltered.

3. A simultaneous increase or diminution in density both of corpuscles and plasma, with or without alteration in the number of corpuscles in a given volume of blood.

Schmaltz, from observations with his capillary pycnometer, concludes that, broadly speaking, the specific gravity of the blood varies directly as the percentage of hemoglobin, but is largely independent of the number of red corpuscles. Hayem states that the specific gravity depends on the corpuscular richness of the blood—the difference possibly being caused by the passage of a certain amount of plasma into the lymph spaces. Dr. Lloyd Jones expresses somewhat the same opinion. Certain experiments of my own appear to show that, in the healthy animal at any rate, a rise of density of the blood, produced artificially, is accompanied by a somewhat closely corresponding rise in the number of red corpuscles.
These experiments further show that so long as the density remains unaltered, even under abnormal circumstances, the number of the corpuscles may also remain practically unaffected.

Again, in cases of paroxysmal hæmoglobinuria, when, during the paroxysm, the red corpuscles are broken up and the dissolved hæmoglobin has escaped from the blood, the diminution in number of the corpuscles is accompanied by a concurrent fall of the specific gravity of the blood; as the following observations show:

<table>
<thead>
<tr>
<th></th>
<th>Specific Gravity of the Blood</th>
<th>No. of Red Corpuscles.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before paroxysm</td>
<td>1.0523</td>
<td>3,910,000</td>
</tr>
<tr>
<td>After</td>
<td>1.0515</td>
<td>3,680,000</td>
</tr>
<tr>
<td>Before</td>
<td>1.0575</td>
<td>3,710,000</td>
</tr>
<tr>
<td>After</td>
<td>1.0505</td>
<td>3,440,000</td>
</tr>
<tr>
<td>Before</td>
<td>1.0518</td>
<td>3,270,000</td>
</tr>
<tr>
<td>After</td>
<td>1.0506</td>
<td>2,970,000</td>
</tr>
<tr>
<td>After</td>
<td>1.0470</td>
<td>2,760,000</td>
</tr>
</tbody>
</table>

I have also shown that the specific gravity of the plasma itself usually falls concurrently with that of the total blood; this being especially the case after experimental injections into the blood-vessels, and in those cases in which the specific gravity of the blood as a whole has been lowered by hæmorrhage. It is also very noticeable in severe cases of pernicious anæmia. At the same time there can be no doubt that in the lowering of specific gravity which may occur under these various circumstances, the substance of the coloured corpuscles has its share of the additional amount of water, and that these corpuscles themselves also become of less specific gravity than previously.

If we desire to observe the specific gravity of the blood serum or plasma we may use Roy’s method, the blood having previously been centrifuged in capillary tubes.

Professor Sherrington thus describes his method of obtaining the serum or plasma from small quantities of blood:—“A drop of blood, as it exudes from a prick in the skin, is taken by capillarity into a fine freshly-drawn glass tube, like a vaccine tube but longer, and bent into a U-shape. The capillary U-tube is then placed, with its bent end downwards, into a ‘bucket’ on the centrifuge, or on a radial slot on a vulcanite disc; the two open ends will then be toward the centre of rotation, and in a few minutes after the instrument is set in action a clear layer of serum or plasma is obtained in each limb of the tube.”

Sherrington and myself have examined the specific gravity of the blood of a number of cases in well-marked anæmia; more than a hundred cases have been observed, with the results given in the appended table. Observations on other diseases have not been by any means so many, but the results are given for purposes of comparison. The observations were taken for the most part at the same time of day, about 11 A.M., a point which Lloyd Jones has shown to be of importance. For comparison certain results arrived at by Quincke and others, working with the older methods, are also brought together in the table, as
well as some of those obtained by Lloyd Jones, who worked with Roy’s method.

In the table the numbers on each side of a hyphen denote the maximum and minimum of the observations relating to the particular diseases; where one number only is given, this is the only one recorded.

Specific Gravity of the Blood in Various Diseases.

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia : Chlorosis ¹</td>
<td>1041–1043</td>
<td>1032–1045 (severe cases)</td>
<td>1035·2 – 1049·1 (probably included cases of pernicious anaemia)</td>
<td>1045·8 (mean of observations on six chlorotic girls)</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>1027–1034</td>
<td>1029–1040</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucocytæmia</td>
<td>1048·5–1051 (1 case in last stage) = 1032</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>1038 (very anæmic)–1050·5</td>
<td>1062</td>
<td>1044·3 (1036 – 1049·5 Robertson) range of five cases</td>
<td></td>
</tr>
<tr>
<td>Lymphadenoma</td>
<td>1067–1057</td>
<td>1035–1052</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haæmoglobinuria Cardiac (none congenital)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1058–1061</td>
<td>1046–1052</td>
<td></td>
<td>1052·5 (mean of series of 24 cases)</td>
</tr>
<tr>
<td>Cirrhosis of liver with ascites</td>
<td>1041–1057</td>
<td>1038–1060</td>
<td></td>
<td>1050·2 (mean of series of 31 cases in third stage)</td>
</tr>
<tr>
<td>Acute nephritis</td>
<td>1054·5–1060</td>
<td>1034·5–1060</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic nephritis</td>
<td>1052</td>
<td></td>
<td></td>
<td>1047·3–1048·7</td>
</tr>
<tr>
<td>Uremia</td>
<td>1048·5</td>
<td></td>
<td></td>
<td>1050·5</td>
</tr>
<tr>
<td>Tuberculosis (of kidney)</td>
<td>1057–1059</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculous peritonitis</td>
<td>1046–1054</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chorea</td>
<td>1052–1047</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic hip disease</td>
<td>1042–1047</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysentery</td>
<td>1049–1052</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic plumbism</td>
<td>1031</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myædema</td>
<td>1058–1062</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

It is worth noting that it is not possible in some cases to form a correct judgment of the probable specific gravity of the blood from the appearance of the patient, as, under certain circumstances at present but ill understood, the tint of the skin is not always indicative of the poorness or richness of the circulating blood. Oppenheimer, in the course of a series of observations on the enumeration of the blood corpuscles with

¹ Schmaltz, using his capillary pycnometer, found the blood in chlorosis possess a specific gravity of 1030–1049 (29 cases). But he apparently includes cases of pernicious anaemia.
the haemocytometer, frequently came across such apparent discrepancies, which he attributes to irregular circulation.

**Shock.**—In the condition known as "shock," which is apt to supervene, to a greater or less degree, on serious injuries and on surgical operations—more particularly when the contents of the abdominal cavity are in any way interfered with—the specific gravity of the blood becomes raised, sometimes to a marked extent, as was first demonstrated experimentally by Sherrington and Copeman. This observation has since been abundantly corroborated by the result of the investigations of Grünbaum and others on the human subject. It is thus apparent that valuable information as to the condition of a patient subsequent to severe accidents or operations is obtainable by examination of the specific gravity of the blood. A well-marked rise of specific gravity, under the conditions indicated, is of distinctly unfavourable import. (See Art. "Shock and Collapse," vol. iii. p. 320.)

**III. Estimation of the Colouring Matter in the Blood.**—Various methods have been elaborated from time to time for the estimation of haemoglobin, but the colorimetric method is the only one which is sufficiently rapid for clinical purposes. Of the colorimetric instruments, devised for these estimations, those best known are Gowers' and v. Fleischl's. The latter apparatus is in general use on the Continent and in America, while, not unnaturally perhaps, the former is better known and more often employed in England. Although both these instruments require brief description, yet it is probable that they will be abandoned before long in favour of a more accurate haemoglobinometer recently introduced by Dr. Oliver. In the colorimetric method a more or less diluted blood solution is compared with a colour standard which, in Oliver's and v. Fleischl's instruments, consists of tinted glass, and in that of Gowers of a glycerine-and-water solution of picric acid and piccarmine solidified with gelatine. In the first two cases a definitely diluted blood is compared with standards of varying intensity, while in the third the blood solution is gradually diluted until its tint corresponds with that of the fixed standard. If any approach to accuracy in the results is to be looked for in the use of any of these instruments, we must provide—

(i.) A standard light.
(ii.) A reflecting surface of standard tint.
(iii.) A means of cutting off extraneous light.

(i.) The employment of a standard light is of special importance since the results obtained will vary with the nature, and, to some extent, with the intensity of the illumination. As it is practically impossible to ensure in every series of observations made by different persons that the source and intensity of the light employed shall be identical, it is desirable, in recording the results of haemometric observations, that a note of the nature and position of the light employed should be appended. On this point Dr. Oliver strongly insisted in his Croonian lectures for 1896, in which he
demonstrated, by means of curves, the extraordinary divergence in colour-value of progressive dilutions of blood when estimated, by means of Lovibond's graded glass colour standards, in daylight and by candle-light respectively.

The colour-curves drawn up by him are made by entering the colour units on the side of the diagram to form abscissae with the standard gradations which appear at the foot. By daylight (Fig. 11) it will be observed that the colour-curves of the blood are made up of varying proportions of red, orange, and yellow. In the lower percentages (10, 20, 30, and 40) red does not exist as a separate colour; it is only present in combination with yellow, as an orange made up of equivalent proportions of each. In these lower gradations the place of red is taken by yellow.

![Fig. 11.—Specific colour-curve of blood, daylight (Oliver).](image)

Between gradations 40 and 50 yellow dies out, and then red appears and increases progressively until at the highest grade it is the dominant colour. In these daylight gradations the curve of orange is the predominant one, though it begins to die out in the higher part of the scale. By candle-light (Fig. 12) the colour-curves are quite different and are less complicated.

Red is predominant throughout, except at the lowest grade, where it is subordinate to orange. From this point upwards orange gradually diminishes, and at 90 vanishes entirely; the highest grades are distinguished by pure red. The remarkable difference between the colour-curves furnished by the two kinds of light is doubtless due to the preponderance of yellow in the candle-flame.

Again, as Mr. Lovibond had previously observed in the matching of some of the aniline dyes, Dr. Oliver finds that the solution of blood possesses the quality of colour-purity, as distinct from colour-depth and colour-composition, or brilliancy in a remarkable degree; for it remains after these others have been duly matched. In the haemoglobinometer devised
by him this difficulty is met by using one of the lower grades of the blue glasses as a cover-glass to the blood-cell—an adjustment which does not disturb the correct reading of the haemoglobin.

(ii.) Whatever source of light be employed the rays should be reflected from a "dead" surface of a pure white colour. In the instructions sent out with Gowers' hemoglobinometer, it is suggested that the estimation should be made by holding the tubes between a white cloud and the eye of the observer; or that light should be reflected from a sheet of white paper held at an angle with the tubes. Sherrington, in measuring the amount of haemoglobin in the blood by the Gowers' instrument, employs the light of a Welsbach lamp reflected from a vertical sheet of white paper not otherwise illuminated. To secure absolute uniformity of tint in the reflecting surface Lovibond uses pure, freshly precipitated calcium sulphate compressed into a slab. This material, which answers admirably, has been adopted in the construction of Oliver's and v. Fleischl's haemoglobinometers.

(iii.) Increased accuracy in hemometric observations may also be obtained by examining the blood solution and the colour standard through a tube of metal, or other material, of about ten inches in length and blackened within. The exclusion of outside light is thus ensured as well as the maintenance of a definite distance between the observing eye and the objects to be compared.

Oliver's hemoglobinometer.—This apparatus is an adaptation to hemometric work of the tintometer, an instrument invented some years ago by Mr. Lovibond of Salisbury for the purpose of estimating with scientific accuracy the true colour intensity of different substances, whether solid or liquid, which are employed in various manufacturing processes. As in

---

**Fig. 12.**—Specific colour-curve of blood, candle-light (Oliver).
the original instrument, use is made of tinted glass standards, with which the solution of blood, diluted to a definite degree, is compared by light reflected from a surface of pure calcium sulphate—the examination being made through a camera tube to exclude outside light.

With the tintometer which, before the introduction of Oliver’s instrument, had been employed by myself for some years past in the estimation of the colour intensity of the blood, three sets of definitely graded glasses are provided; one for each of the dominant colours, red, yellow, and blue. The graduations in each set are of equivalent value, the test of which is the production of a neutral tint when equivalent grades of the three colours are mixed. On the other hand, any shade or degree of colour can be matched by appropriate combinations of non-equivalent grades, and the measurement thus made can be recorded numerically and so reproduced at will. By means of Lovibond’s standards Oliver has determined the colour value of progressive dilutions of normal blood by uniform candle-light, and also by daylight. Corresponding to these values he provides a series of glass standards by comparison with which the percentage colour-intensity of any sample of blood can be read off at once. Oliver has done good service in so simplifying the use of the tintometer that, while his modification is much more compact and so more readily applicable to clinical work, all the essential points of the original instrument are retained. In the hæmoglobinometer, however, provision is made for utilising a double instead of a single transmission of light through the blood solution and the standard glasses. The originator of this method asserts that greater accuracy of estimation is rendered possible when such double transmission of light is utilised, especially if working with specimens which, as in the case of blood obtained from cases of severe anæmia, present a low colour intensity. On the other hand, when the colour more nearly approaches normal it is possible to carry out an estimation with half the quantity of blood that would otherwise be requisite.

The apparatus as sent out for use consists of—(i.) an automatic blood-measure; (ii.) a mixing pipette; (iii.) the blood-cell and cover-glass; (iv.) sets of standard gradations; (v.) riders; (vi.) the camera tube; (vii.) standard candles; (viii.) a bottle of antiseptic fluid, a lancet, needles, and thread.

(i.) The automatic blood measure has a capacity of 5 c.m.m., and fills readily by capillary attraction. It is made of stout glass, and the end presented to the blood is well polished, so that all traces of blood can be removed from it by the finger. The bore is dried out before an observation by passing a needle through it threaded with darning cotton. The handle is useful for stirring together the blood and water in the blood-cell.

(ii.) The mixing pipette is provided with a rubber nozzle which fits over the polished end of the blood-measurer, and ensures the complete rinsing out of the blood with the first few drops of water.

(iii.) The blood-cell is of more than sufficient capacity to ensure the complete liberation of the hæmoglobin. When filled level with the rim it yields a blood solution of rather less than 1 per cent. It is itself the VOL. V
measure of the amount of water to be added, and it is quite easy to fill it accurately.

Fig. 18.—Oliver's hemoglobinometer.  a, Sets of standard colour grades; b, guarded lancet; c, automatic blood-measure; d, mixing pipette; e, blood-cell and cover-glass.

(iv.) The standard gradations are arranged as circular discs in two slabs, six in each; and they represent divisions of 10 degrees of the scale from 10 to 120 inclusive.
(v.) The riders are small squares of tinted glass provided for the reading of the degrees between each standard gradation. In use the slip of colourless glass is placed over the cover of the blood-cell, so as to balance the effect of the layer of glass of the rider which is laid over the standard. Two sets of riders have been arranged; one suitable to ensure the finer readings—for example, of 1 degree for physiological observation, and the other, sufficient for ordinary clinical observation, to enable the observer to determine differences of 2 degrees. For the reading of the units nine riders are required, which are grouped into three slides. It should be premised that the value of the riders is neither the same in the two standards required for candle-light and daylight, nor in the upper and lower halves of either standard. This want of uniformity arises, as previously stated, from the differences of the specific colour-curves in the two standards, and in the two portions of each. In the transition grades—the lowermost of the upper half and the uppermost of the lower half—this rule does not accurately apply; but inasmuch as the departure is constant in all observations, and is moreover slight, it may be disregarded for the sake of simplicity.

The daylight standard is less well adapted to the finer readings than the candle-light one, because the value of each rider becomes equal to 2 degrees in the upper half of the scale and 4 degrees in the lower half; and when candle-light is used each rider has an equivalent value in the six stronger grades of 1 degree and a double value in the six weaker grades of 2 degrees. For ordinary readings one rider only is used, namely, that which is equivalent to 5 degrees in each slab of the standards. Therefore each set of six standard gradations, whether for candle-light or daylight, has its own rider. When the blood solution is deeper in colour than any particular standard gradation, but is over-stepped by the rider, the mean between the two may be taken as the reading; and the same rule will apply when the colour of the blood is higher than the rider, but is not so high as that of the next standard grade above. Hence this single rider may be made to provide readings of 0.25 and 0.75.

(vi.) The camera tube.—A tube of simple construction is provided which, being collapsible, will pack into a small compass with the other parts of the apparatus.

(vii.) The standard candles are of such a size as to afford a suitable and sufficiently uniform intensity of light. The position of the candle should be such as to furnish a high light, the flame being three or four inches above the cells. The observer will soon learn how to adjust the distance to the best advantage, so as to match the colours with the greatest certainty and accuracy. The actual distance does not affect the reading; but if the candle be placed too near, the glare becomes distractingly strong, especially when the lower grades, which require less light than the higher, are under observation.

The bore of the blood-measurer is first dried with the needle and cotton, and the polished point is presented to the drop of blood. The pipette must
be quite filled, and if more than one application to the drop be needed, there must be no break in the column of blood. Any blood adhering to either end must be carefully wiped away with the finger. The rubber nozzle of the mixing pipette, charged with water, is now adjusted over the polished end of the pipette, and the blood washed into the blood-cell by pressing through the water drop by drop. The handle of the pipette is then used as a stirrer, and further additions of water, if required, are made so to

impinge upon it as to graduate the size of the drops required to fill the cell accurately. It is easy to do this when the observer catches the reflection of a window on the surface of the fluid. A final thorough mixing with the handle will be required, and, to secure a level filling, another slight addition of water may be necessary. The cover-glass is then adjusted, when the presence of a small bubble signifies that the cell has not been overfilled. Finally, the blood-cell is placed by the side of the standard gradations, and the eye quickly recognises its approximate position on the scale. If the blood solution be matched in depth of colour by one of the standard grades the observation is at an end; but if it be higher
than one gradation, but lower than that above it, the blood-cell is placed opposite to the former and riders are added to complete the estimation. It is advisable to take a standard time, say ten seconds, for looking down the tube. If the eyes are strained with long working, it is well to look for a moment on the inside of the lid of the instrument case, which is lined with green morocco, complementary in colour to the blood and the colour-standards. This change rapidly restores the acuteness of observation.

In the more elaborate form of tube employed by Dr. Oliver the eyepiece is provided with a collar into which is let a piece of green glass. He finds that the most delicate appreciation of difference between the

![Diagram of Gowers' haemoglobinometer]

**Fig. 15.—Gowers' haemoglobinometer.**

A, Bottle with pipette stopper for holding the diluting solution; B, capillary pipette for measuring the blood; C, graduated tube for measuring the amount of hemoglobin; D, standard tint of normal blood; E, support for D and C; F, puncturing needle.

tints of the blood solution and of the standard is obtained by from time to time intercepting the impression of the discs by the finger, while the candle-flame is viewed for a few seconds through the green glass.

**Gowers' haemoglobinometer.**—This instrument consists of two small glass tubes of the same size. One contains a standard tint corresponding to a dilution of 20 cubic mm. of blood in 2 cubic centimetres of water (1 in 100); the standard is made of glycerine jelly tinted with carmine and piccocarmine. The second tube is graduated, so that 100 degrees are equal to 2 centimetres (100 times 20 cubic millimetres).

Twenty cubic millimetres of blood are measured by a capillary pipette (similar to, but larger than that used for his haemocytometer), and after placing a few drops of distilled water in the second tube, this quantity of the blood is ejected into the bottom of it. The mixture is rapidly agitated by a rinsing action, and distilled water is then added, drop by drop, from the pipette stopper of a bottle supplied for
that purpose, until the tint of the dilution matches that of the standard. The amount of added water indicates the amount of haemoglobin present. As average normal blood yields the tint of the standard at 100 degrees of dilution, the number of degrees of dilution necessary to obtain the same tint with a given specimen of blood is the percentage proportion of the haemoglobin contained in it. For instance, let 20 cubic millimetres of blood from an anaemic patient give the standard tint at 30 degrees of dilution, this specimen would contain only 30 per cent of the normal quantity of haemoglobin. By ascertaining the corpuscular richness of the blood with the haemocytometer we can compare the two. A fraction, of which the numerator is the percentage of corpuscles, gives at once the average value per corpuscle. Thus, if the blood containing 30 per cent of haemoglobin contain 60 per cent of corpuscles, the average value of each corpuscle is \( \frac{3}{6} \), or one-half of the normal. Sir William Gowers suggests that in using the instrument the tint be estimated by holding the tubes between the eye and a window, or by placing a piece of white paper behind the tubes. Care must be taken that the tubes are always held in the line of light, not below it, as in the latter case some light is reflected from suspended corpuscles from which the haemoglobin has been dissolved. If all the light be transmitted directly through the tubes the corpuscles do not interfere with the tint. During 6 or 8 degrees of dilution it is difficult to distinguish a difference between the tint of the tubes; it is necessary, therefore, to note the degree at which the colour of the dilution ceases to be deeper than the standard, and also that at which it is distinctly paler. The degree midway between these will represent the haemoglobin percentage. The instrument is accurate within 2 or 3 per cent.

In order to obtain the greatest amount of accuracy in determinations of the haemoglobin power of specimens of blood by means of Gowers’ instrument, it is desirable not only to compare the tint of the contents of the two tubes by the aid of a standard artificial light reflected from a white surface, but also to cut off extraneous light as much as possible. With the old form of this instrument the writer finds that this may be effectually done by fixing an upright metal screen to the base in which the tubes are supported. This screen should have two narrow perpendicular slits corresponding to the central portion of the tubes; and it is well to have a movable slide of metal, working in the slits, which can be brought down level with the uppermost point at which the diluted blood stands in the graduated tube.

In the newer form recently brought out by Messrs. Hawkley an attempt is made to produce a similar effect by flattening the tubes, so that their contents present a more uniform tint from edge to edge, and by fixing the tubes in their support parallel to one another, but diagonally across the stand instead of side by side.
By looking at them in the proper position their adjoining edges appear to overlap, and as no white light is visible between the two tubes their respective tints can be more accurately compared.

v. Fleischl's haemoglobinometer. — This instrument consists of a small metal stage, somewhat like that of a microscope, having on its upper surface a metal cylinder 1½ centimetres in length, which is open above and closed beneath by a glass plate, and is divided by a vertical metal partition into two equal parts. Beneath the stage a movable metal frame supports a long and narrow wedge-shaped slab of coloured glass, the colour ranging from deep red purple at the thickest end to clear glass at the opposite end.

The frame supporting the glass wedge moves on a rack and pinion attachment in a horizontal direction, so that every portion of the wedge can be brought in succession beneath the base of one of the cells formed by the divided metal tube. This portion of the cylinder is intended to be filled with water, the other half with diluted blood. By means of a reflector, the face of which is formed of a layer of pure calcium sulphate, light is directed upwards through the two cells. The source of light...
should always be a standard one, such as a Welsbach burner of known illuminating power—artificial light being, for several reasons, much better than daylight.

Capillary pipettes, for measuring the requisite amount of blood, are supplied with the instrument, their capacity being such that, when healthy blood is used, the colour of their contents on dilution to the requisite extent corresponds to that of the portion of the red glass wedge opposite the 100 graduation.

One of the pipettes, held by means of a short and flattened wire handle, is first completely filled with blood by capillarity, the pipette being afterwards carefully wiped to remove any blood from its sides or ends. Without loss of time the blood is transferred, by means of a to-and-fro motion, to one of the compartments of the divided metal cylinder, into which a few drops of water should previously have been poured. The expulsion of the blood from the pipette may be aided by pressing through it a drop or two of water by means of a glass tube provided with an indiarubber nozzle. Both compartments are now to be completely filled with water, that containing blood also being carefully stirred by means of the pipette handle, to ensure thorough mixture of the contents. Care must be taken that the fluid in one cell does not overflow into that in the adjoining cell, and that the metal cylinder is so placed in position on the stage that the base of the cell containing water is situated exactly over the coloured wedge of glass, while the light thrown upwards from the reflector reaches the eye through both compartments in equal amount. By means of the rack and pinion adjustment the wedge of glass is now moved backwards or forwards until the colours in both compartments of the cylinder correspond. The frame carrying the glass wedge is graduated along one side, and the number denoting the percentage of haemoglobin in the specimen of blood under examination is read off directly through a small opening in the upper surface of the stage. It is by no means easy, however, to match the colour of the blood solution accurately, for reasons that have already been stated; and this is particularly the case when the amount of haemoglobin in the blood is small. The graduation of the instrument is also somewhat inaccurate, percentages of 80 or 90 only being usually shown in examination of blood which is apparently normal. Cabot recommends the observer to look at the "divided cylinder" from one side, so that the image of the two cells shall fall on the lateral instead of on the upper and lower portions of the retina; under which circumstances, he says, a more correct judgment is possible. He further advises that the source of light should be placed at such a distance from the instrument as to reduce the intensity to a point barely sufficient for the estimation. Comparison of the colour value of the blood solution with that of the glass wedge will also be easier if both be observed through a tube or roll of paper blackened on the inside.

IV. ENUMERATION OF THE BLOOD CORPUSCLES.—This method consists in the dilution of the blood to a considerable but known extent, and the
subsequent counting, under the microscope, of the number of the corpuscles in a small and measured amount of such diluted blood. A comparatively simple calculation will then enable us to estimate the number present in any given bulk of the blood originally taken for our purpose. In both of the modes, which will be described in detail, the corpuscles in the small sample of diluted blood are reckoned by means of a series of micrometer squares ruled over a certain area of the glass floor of the chamber or cell.

In Gowers' hemocytometer, the instrument which up to the present has been in most general use in England, measured quantities of blood and of the appropriate diluting solution are drawn up in a couple of pipettes of known capacity, the mixture being afterwards effected by blowing out the contents of each of the pipettes into a small glass pot in which they are thoroughly stirred. In the Thoma-Zeiss instrument one pipette serves not only for the measurement both of blood and diluting solution, but also for ensuring the subsequent admixture of one with the other. The exact composition of the fluid employed for dilution of the blood is to some extent a matter of indifference, provided that it be of such a nature as not to act injuriously on the corpuscles, and of such specific gravity that the corpuscles readily sink in it. A normal saline solution (NaCl 0·7 per cent in distilled water) serves the purpose; or a solution of sulphate of soda having a specific gravity of 1025, as suggested by Gowers, may be employed. Other useful solutions are the following:

**Hayem's Fluid.**

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercureic bichloride</td>
<td>0·25 gram.</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>0·5</td>
</tr>
<tr>
<td>Sodium sulphate</td>
<td>2·5 grams.</td>
</tr>
<tr>
<td>Distilled water</td>
<td>100·0 c.c.</td>
</tr>
</tbody>
</table>

**Thoma's Fluid.**

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic acid</td>
<td>0·3-0·5 c.c.</td>
</tr>
<tr>
<td>Distilled water</td>
<td>100 c.c.</td>
</tr>
</tbody>
</table>

Recommended by Thoma as useful in the determination of the number of leucocytes, the red corpuscles being dissolved by the acetic acid.

**Toisson's Fluid.**

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl violet</td>
<td>0·025 gram.</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>1·0</td>
</tr>
<tr>
<td>Sodium sulphate</td>
<td>8·0 grams.</td>
</tr>
<tr>
<td>Glycerine</td>
<td>30·0 c.c.</td>
</tr>
<tr>
<td>Distilled water</td>
<td>160·0 c.c.</td>
</tr>
</tbody>
</table>

The addition of the methyl violet or other aniline dye facilitates the counting of the white corpuscles by staining them, and so rendering them more conspicuous.
Sherrington's Fluid.

| Ehrlich's purified methylene blue | 0.1 grm. |
| Sodium chloride                   | 1.2 "    |
| Neutral potassium oxalate         | 1.2 "    |
| Distilled water                   | 300.0 c.c. |

In this solution both chromocytes and leucocytes may be studied for an almost indefinite length of time without losing their characteristic appearances, especially if the examination be carried out on the warm stage.

![Diagram of Gowers' hemocytometer]

**Fig. 18.**—Gowers' hemocytometer.

A, Pipette for measuring the diluting solution; B, capillary tube for measuring the blood; C, cell with divisions on the floor, mounted on a slide, to which springs are fixed to secure the cover-glass; D, vessel in which the solution is made; E, spud for mixing the blood and solution; F, guarded spear-pointed needle.

Gowers' hemocytometer.—This instrument, a modification by Sir W. R. Gowers of that originally devised by MM. Hayem and Nachet, consists of (a) a small pipette, which, when filled to the mark on its stem, holds exactly 995 cubic millimetres—this pipette is furnished with an indiarubber tube and mouthpiece to facilitate filling and emptying; (b) a capillary tube marked to contain exactly 5 cubic millimetres; also filled with an indiarubber tube and mouthpiece; (c) a small glass jar in which the dilution is made; (d) a glass stirrer for mixing the blood and solution in the glass jar; (e) a brass stage plate, carrying a glass slip on which is a cell one-fifth of a millimetre deep. The floor of this cell is divided by ruled lines into one-tenth millimetre squares. Upon
the top of the cell when in use rests a cover-glass, which is kept in its place by the pressure of two springs fixed to uprights at each end of the stage plate.

The instrument is employed as follows:—995 cubic millimetres of the solution are first placed in the mixing jar, after which 5 cubic millimetres of blood are drawn into the capillary tube from a puncture in the finger, and then blown into the solution. The two fluids are well mixed by rotating the stirrer between the thumb and the finger, and a small drop of this diluted blood is placed in the centre of the cell. The cover-glass is now gently lowered upon the cell and secured by the two springs, after which the plate is placed upon the stage of the microscope. The lens is then focussed for the squares. In a few minutes the corpuscles will have sunk to the bottom of the cell, and are seen at rest on the squares. The number is then counted, and the cubic area of diluted blood over each square is of such amount that this multiplied by 10,000 gives the number in a cubic millimetre of blood. Taking 5,000,000 corpuscles as the average per cubic millimetre for healthy blood, the average number in two squares of the cell is 100. Consequently the number of corpuscles present in two squares (ascertained by counting a larger number, such as 10 or 20, and taking the mean) expresses the percentage proportion of the corpuscles in the specimen of blood under observation to that of health; or, made into a two-place decimal, the proportion which the corpuscular richness of the specimen bears to that of normal blood taken as unity. In making such examination a sufficiently large drop of blood must be obtained by puncture with the point of the lancet without the employment of much pressure, for if the finger be much pressed or squeezed or ligatured, the relative amount of serum and corpuscles contained in the sample of blood abstracted is liable to be affected, and thus to afford inaccurate and consequently valueless results. It is somewhat difficult to draw the exact quantity of blood into the capillary tube, because in removing the blood from its point a little is easily drawn out of the tube; it is therefore better to draw rather more than the required quantity into the tube, then to remove the blood from the point with a soft cloth, and keep the cloth in contact with the point while the extra blood is blown out. A little of the diluting fluid should be drawn into the tube after the blood is ejected to ensure the removal of all the corpuscles. The smaller end of the stirrer may be used to remove the drop of diluted blood from the mixer to the cell. This drop must be deposited in the middle of the cell over the ruled squares, and care must be taken not to rub the stirrer on the engraved portion of the floor. The lines which form the divisions of the micrometer cell may be made more distinct in the following manner:—With a sharp penknife scrape a little of the lead of an ordinary soft lead pencil so that it falls into the middle of the micrometer cell, then, with a clean dry finger-tip, or a knot tied in a small piece of chamois leather, rub the powdered lead well over the cell; it may then be wiped in the ordinary way, and any of the lead which remains in the corners of
the cell easily dusted away with a camel-hair brush. Powdered carmine may be employed in a similar fashion.

The cover-glass should be held in a horizontal position as it is being lowered on to the cell. When this has been done, the drop of solution should appear as a disk as nearly as possible in the middle of the cell, and care must be taken that the fluid does not run to the sides of the chamber. The two springs are to be carefully placed opposite each other by lifting them on the cover-glass, and not by "sliding" them.

Gowers advises that the corpuscles should be counted in or near to the centre of the drop, and says that by raising the objective out of focus the white cells may readily be distinguished by their greater refractive power. A light which should not be too intense, and the position of which is so arranged that the rays when reflected upwards pass diagonally across the squares, will give the best illumination for both sets of lines. The whole process from beginning to end need not occupy more than a quarter of an hour.

The blood should not be drawn until the diluting solution has been placed in the mixing jar and the capillary tube is ready for use. The blood should be expelled immediately, as otherwise it may coagulate. Immediately after use, the pipette and capillary tube should have clean water drawn up into them; this may be followed by alcohol and ether if rapid drying be necessary. If either be obstructed, a horse hair or a piece of fine brass wire will probably clear it; or it may be cleared by placing it in nitric acid, all trace of which must afterwards be removed with water. In standardising the pipettes, the residual fluid, that which unavoidably adheres to the inner walls of the tubes, has been allowed for, so that the quantity ejected is exactly that indicated by the division upon each tube.

The cell must be cleansed after each observation by means of a small camel-hair brush and some clean water, after which it is dried carefully with a soft cloth. The cell must never be used a second time whilst damp, or the globule of fluid will at once disperse over its surface, and the corpuscles will not be deposited evenly over the floor.

The Thoma-Zeiss haemocytometer is in most general use for the enumeration of the blood corpuscles on the Continent and in America. As in Gowers' haemocytometer, the essential parts of the instrument consist of a counting-chamber and of a measuring pipette, which serves the double purpose of taking up the required amount of blood and of enabling it to be mixed with a definite quantity of the diluting fluid. The counting-chamber is formed of a glass slide supporting a square glass cell with a central circular aperture. Within this is fixed
a smaller disc of glass ruled on its upper surface into a series of microscopic squares; the thickness of the disc being such that, when an accurately ground cover-glass is lowered over the aperture of the square cell, an interval of exactly 0.1 millimetre is left between the adjoining faces of cover-glass and disc.

The little moat which separates the internal edge of the cell wall and the periphery of the disc serves to catch any excess of fluid for which there may not be room in the space between the disc and the cover-glass. The size of each square is the \( \frac{1}{100} \) of a square millimetre, the individual lines being exactly \( \frac{1}{10} \) of a millimetre apart. The area over each ruled square has then the value of \( \frac{1}{10000} \) of a cubic millimetre. The small squares are marked into groups of sixteen by means of more thickly ruled lines; these larger squares being very useful in reckoning the white corpuscles.

The diluting pipette consists of a thick-walled capillary tube which towards its upper end expands into a bulb, above which the pipette has again its capillary bore. Contained within the bulb is a small bead of glass for the purpose of facilitating the admixture of blood with the diluting solution. The lower extremity of the pipette is bevelled to a point and polished so that any excess of blood, or other fluid, clinging to it can easily be wiped off with a soft cloth. The portion of the pipette below the bulb is ruled off by cross lines marking tenths from 0.1 to 0.5 and 1; while above the bulb the mark 101 is found.

When using the apparatus the point of the pipette is applied to a drop of blood obtained in the manner previously described. By gentle suction, through an indiarubber tube attached to the upper portion of the pipette, blood is drawn up to the 0.5 or the 1 mark; after which the diluting solution is also drawn up until the mark 101 is reached, by which a dilution of the blood of 1 in 100 or 1 in 200 is obtained, according to whether the half or the whole of the capillary portion of the pipette has
been filled with blood. The pipette is then gently rotated in the fingers for about a minute in order to ensure thorough admixture of the contents of the bulb, the process being aided by the presence of the little bead of glass. It is a matter of some little difficulty to draw up into the pipette exactly the amount of blood required. For this reason it is well to employ the dilution of 1 in 200, as in case the amount of blood obtained at the first attempt should reach slightly above the 0.5 graduation, the quantity in excess can be got rid of again by gently blowing through the tube; whereas if the higher mark should be exceeded and blood escape into the bulb it is useless to continue the operation until the whole pipette has been most carefully cleaned out and dried. Moreover, if the blood be of fairly normal quality, the number of red corpuscles in it will be so crowded over the surface of the ruled squares as seriously to interfere with the ease and accuracy of the counting.

Professor Sherrington finds that the greatest amount of accuracy in the enumeration of the blood corpuscles is to be obtained by the use of the Abbé-Zeiss counting-chamber in conjunction with the pipette made by Hawksley, instead of the one (devised by Thoma) which is usually sent out with the instrument.

According to Sherrington, the objections to the Thoma pipette are the large internal surface relatively to cubic content, the difficulty of drying the bead in the mixing-chamber quickly enough for use in successive observations, and the presumption that leucocytes will adhere to the bead. These objections are obviated in the new form of pipette containing no bead, and possessing a wider bore than the Thoma instrument. Sherrington also lays much stress on the importance of counting both chromocytes and leucocytes in the same film of the diluted blood; and of enumerating in the same film the representatives of the various leucocytes distinguishable when this step is considered necessary. And there can be no doubt that this plan is much preferable to that of counting the chromocytes in one film, the leucocytes generally in a second, and of determining the numerical proportion of their different varieties in yet another. It must, however, be borne in mind that it may not be possible to obtain Ehrlich's colour reactions with a living film.

When counting the leucocytes with the Thoma-Zeiss apparatus it is usual to dilute the blood ten times only; under which conditions the chromocytes must be rendered invisible in some manner, as otherwise their number tends to obscure the leucocytes. This difficulty may be overcome by employing Thoma's 0.3 acetic acid solution for diluting the blood; this having the effect of "laking" the chromocytes.

After a time, however, the leucocytes are also affected by the acid, so that it is better to dilute the blood to a larger extent and to enumerate both chromocytes and leucocytes at the same time. With care and practice this can be done if the dilution is carried out in the proportion of forty-nine parts of solution to one part of blood. In order to render the leucocytes more obvious I have been accustomed for many years past to dilute the blood with normal saline solution just tinged
with a few drops of a watery solution of some aniline dye; but for this purpose the mixture devised by Sherrington (p. 442) is preferable, as the blood corpuscles remain entirely unaltered in it for considerable periods.

When the leucoeytes are enumerated in a fifty-times diluted blood, as suggested, it is well to obtain an additional basis for calculation, not only by counting those lying on the squares, but also those over the whole of the floor space as far as the ruled lines extend. The area of this enlarged space must previously have been calculated, as it varies somewhat with each instrument.

V. Estimation of the Reaction of the Blood.—Under normal conditions the reaction of the blood, as tested by litmus, is invariably alkaline. Slight variations in the degree of alkalinity can indeed be demonstrated in connection with such physiological processes as the digestion of food, in which the alkalinity of the blood tends to become increased; or as the after-effects of severe muscular exertion, by which, on the other hand, it is for a time somewhat diminished. Even under pathological conditions, however, it is unusual to find any extreme departure from the normal range; and although such variations as have been observed in the course of those diseases in which systematic investigation of the blood reactions have been carried out, show that change is usually in the direction of a fall of alkalinity, it is doubtful whether an acid reaction has ever been demonstrated during life. It is a somewhat curious fact that the reaction of the blood is, for the most part at any rate, dependent on the presence in it of sodium hydrogen carbonate (NaHCO₃) and sodium hydrogen phosphate (Na₂HPO₄), both of which, chemically speaking, are acid salts. As, however, these salts are formed of bases very loosely combined with acids, they are readily dissociated when brought into connection with a substance, such as litmus, which is capable of withdrawing the bases and uniting with them to form a distinctively coloured salt; this colour production serves, therefore, as a test not only for free bases, but also for bases which are combined with weak acids. This latter power is not possessed by certain other substances which are sometimes employed as indicators in alkalimetric investigations, such as phenolphthalein; for this reason they cannot be employed in observations on the reaction of the blood. Fortunately, however, we have in carefully prepared red or neutral litmus an indicator sufficiently delicate (according to the observations of Wright and others) to show an immediate and distinct colour change with normal human serum which has been diluted as much as forty-fold. In all the various methods that have been proposed for the estimation of the reaction of the blood litmus has been employed as an indicator. In the earlier qualitative methods of Leibreich and Schäfer, slabs of plaster of Paris in the one case, and sheets of glazed paper in the other, impregnated with litmus were used, the intention being to retain the blood corpuscles on the surface, from which they could afterwards be washed in order to bring any colour-change into view; meanwhile the
fluid portion of the blood, soaking into the substance of the slab or paper, was thus enabled to react with the previously absorbed litmus.

If it be desired to estimate quantitatively the degree of alkalinity of the blood, it becomes necessary to employ not only an indicator, but also a standardised solution of some acid. In the titration methods first introduced phosphoric acid was employed for this purpose by Zuntz, tartaric acid by Lasser and Landois, oxalic acid by Drouin. Although convenient to prepare, solutions of these organic acids tend to weaken after a time as the result of exposure to light and air; for this reason they have been discarded in favour of suitably diluted solutions of sulphuric acid. Landois' method, as improved by Drouin, is probably that which has been most extensively employed; but it possesses the serious disadvantage that, in order to obviate a difficulty introduced by the presence of the red corpuscles, the blood has to be considerably diluted with solutions of sulphate of soda, by which the estimation of the exact neutral point is rendered somewhat difficult. This objection cannot be advanced against the methods now to be described.

Haycraft and Williamson's method.—This method is a development of the qualitative test originally introduced by Schifer. The alkalinity is estimated by a graduated series of red litmus-papers.

To prepare the papers, place over-night a dozen half-sheets of cream-laid notepaper under a tap of running water in order to remove the acid generally present. Soak the papers in strong neutral litmus and dry them. Neutral litmus-papers may be purchased if desired. Pour a pint of normal (7 c.c. per 1000 c.c. of water) sulphuric acid into a shallow basin, plunge into it for half a minute a sheet of litmus-paper, withdraw it, blot it, and dry it; this is the strongest acid paper.

Now dilute the normal sulphuric acid with an equal volume of water, soak another sheet of litmus-paper, blot, dry, and mark it. Dilute the acid again and again until eight or ten papers are prepared. These should dry in the horizontal plane so that the acid does not gravitate to one border of the paper.

When prepared, the papers must be glazed by passing them between steel rollers. Any large stationer will do this, and the papers are then ready for use. Each sheet may be cut up into strips, or these may be cut off as required.

The method is to cleanse the finger of the patient and to puncture it with a broad-tipped stilette; the blood must not be squeezed from the finger. A paper, say D, is brought in contact with the drop for ten seconds, and then dipped in water. If there is no blue stain try E, and if there is a blue stain try C. The operator will soon find out the paper which just gives a reaction with normal blood, and he will be able in other cases to judge roughly if deviations from the normal are present. This method does not pretend to great exactitude, and may be classed in this respect with some other clinical methods, such as the estimation of chlorides in urine by the subsidence of the precipitate.

1 Communicated by Professor Haycraft.
Undoubtedly Haycraft's method possesses the merit of simplicity, but it has undergone severe criticism at the hands of Hutchison, who has stated that the results afforded by it are apt to show an extraordinary divergence from those obtained by means of the titration method. Thus he finds that the alkalinity of the blood in anaemia, as tested by the method of Haycraft and Williamson, is invariably above normal; and often, apparently, to an excessive degree. On the other hand, when the titration method is employed it is, according to this observer, as invariably found that the alkalinity of the blood is reduced. Hutchison explains this apparent contradiction between the results afforded by the two methods on the ground that the alkalinity of the plasma alone is ascertained by the glazed litmus-paper method, the alkali contained in the corpuscles which are left on the surface of the paper not being estimated, as in the titration method, during the performance of which the breaking down of the corpuscles liberates their contained alkali. Moreover, Hutchison concludes, as the results of experiments, that the more watery the blood the more readily the plasma percolates into the glazed litmus-paper. Under these circumstances the contained acid is more readily neutralised, and a fictitious value is given to the amount of alkali present in the blood. This difficulty cannot be surmounted by allowing the drop of blood to remain for a longer time in contact with the paper, for, as all observers are agreed, the alkalinity of the blood diminishes rapidly after its removal from the body. But the titration method of Landois, which, according to Hutchison, affords an estimate of the total amount of alkali in the blood, requires considerable care in its performance, if this result is to be obtained; since, as Loewy has shown, it is only when the blood is titrated very slowly at body temperature that all the corpuscles are broken down.

With reference to this point, however, it has always appeared to me that since it is the plasma of the blood and not the corpuscles that come into direct relation with the tissues, it is the estimation of the alkalinity of the plasma rather than that of the total blood which is of more immediate interest from the clinical point of view. I have been accustomed, therefore, for the purpose of observations on the reaction of the blood, to employ specimens of plasma (or serum) obtained by centrifuging a few drops of blood in capillary U-shaped tubes, after the manner originally employed by Sherrington and myself when working at the subject of specific gravity. Treated in this manner, a few minutes suffice to separate entirely the corpuscles from the plasma (or serum), portions of which taken up and measured in capillary tubes should then be mixed with exactly similar quantities of varying dilutions of normal sulphuric acid; the reaction in each case being tested by means of sensitive litmus-paper.

Wright's method.—This is a titration method also in which, as is now almost invariably the case, litmus is used as the indicator, and normal sulphuric acid, in appropriate dilutions, to neutralise the alkali of the blood. Unlike Hutchison, however, Prof. Wright maintains that, as the result of
his own observations, as also of those of Drouin, "changes in the alkalinity of the circulating blood invariably manifest themselves in changes of the alkalinity of the serum." Acting on this assumption, therefore, he prefers for hæmalkalimetric observations to employ serum, and preferably that which has exuded from a blood-clot, rather than fresh plasma "contaminated" with red blood corpuscles.

As is, however, agreed on all hands, the alkalinity of blood undergoes a gradual diminution after removal from the living vessels; and consequently Wright thinks it well to postpone the estimation for some hours until, as he believes, a condition of stable equilibrium is reached.

It will be obvious, therefore, that the results obtained by him, although they may be comparable among themselves, do not afford an accurate estimate of the alkalinity of the freshly-drawn blood. On the other hand, if, as I have suggested, the blood be centrifuged, an estimation can be made within a few minutes of its withdrawal; and, in the absence of red corpuscles, the fall of alkalinity, if indeed it occur, is at any rate much less rapid than is otherwise the case, and so may be neglected.

In Wright's method five progressive dilutions—twenty, thirty, forty, fifty, and sixty-fold—of normal sulphuric acid are employed in the titration:

This is performed by first drawing up into a fine capillary tube about one-sixth of the amount of serum available, followed by an equal amount of dilute acid. Accurate measurement is ensured by marking the pipette at the point reached by the serum, tilting it so as to include a bubble of air in the bore, and finally filling it up to the original mark with the acid solution. The exactly equal amounts of serum and acid thus obtained are next blown out into a watch-glass, thoroughly mixed and tested by transferring a series of separate drops to the surface of a strip of red litmus-paper.

If the twenty-fold diluted acid solution has been employed, it will probably be found that in working with normal blood the mixture will show an excess of acid. In this case it will be necessary to proceed, in precisely similar manner, to titrate with each other equal volumes of serum and the thirty-fold diluted solution. Intermediate degrees of alkalinity can be estimated by mixing, in a clean watch-glass, equal volumes of, say, thirty and forty-fold diluted normal acid, and titrating with the resulting thirty-five-fold acid solution. If this dilution should suffice to neutralise the acidity of the given sample of serum exactly, the result is expressed by the fraction $\frac{N}{57}$. Prof. Wright found, as the result of a number of estimations of apparently normal blood, that the serum has an alkalinity which varies between the values $\frac{N}{30}$ and $\frac{N}{45}$, the average being about $\frac{N}{37}$.

It has been shown that during health the constancy of the level at which the alkalinity of the blood is maintained is so great as to suggest that some regulating mechanism must be continuously at work to secure it. And in many diseased conditions the action of this regulating mechanism is disturbed in so slight a degree that no appreciable departure
from the normal slight phasic variations is demonstrable. Under certain circumstances, however, marked alterations may be found; this being specially so in the specific fevers, in the various forms of anaemia, including leukaemia, in diabetes, particularly if coma be about to supervene, in uremia, gout, and jaundice, and in certain cases of poisoning, as for instance by carbonic oxide or potassium chlorate. The alteration that occurs under these conditions is almost invariably in the direction of a lowering of alkalinity, due, as it would appear, to the presence in the blood of various acids, such as lactic, uric, oxybutyric or bile acids respectively, according to the particular disease under consideration. In anaemia, however, and markedly in chlorosis, an increase of alkalinity is usually present, this being the more obvious if it be the reaction of the blood plasma which is estimated rather than that of the total blood.

VI. DETERMINATION OF THE COAGULATION TIME OF THE BLOOD.—When first shed, blood appears to the naked eye as a homogeneous red fluid; but at a longer or shorter interval, after removal from the body, it gradually separates into two portions, consisting of a semi-solid coagulum or clot, which still remains red—though the colour gradually becomes somewhat darker—and a clear straw-coloured fluid, the serum, the amount of the latter gradually increasing as more of it is squeezed out of the interstices of the contracting clot.

The clot consists of a fine meshwork of interlacing filaments of fibrin; the red colour and the chief bulk of the clot being due to the entanglement of the red blood corpuscles amid the threads of fibrin. Fibrin may be obtained free from corpuscles by washing the clot thoroughly under a stream of water until the washings are no longer coloured: the grayish-white, stringy mass which remains is fairly pure fibrin. If coagulation take place more slowly than usual the corpuscles will have time, before the separation of the serum, to sink towards the lower portion of the vessel into which the blood is received; and in such case the upper layer of the clot which eventually appears will be more or less devoid of colour: this portion is what is known as the “buffy coat.”

In certain pathological states, such as haemophilia for instance, the rate of coagulation is important both in respect of the disease itself and of the results of treatment. For clinical purposes the “coagulation time” can be ascertained by allowing a few drops of blood from a finger-prick to fall on a glass slide, taking care that the individual drops remain isolated from one another, and are fairly equal in size. If now a fine and carefully cleansed needle be drawn through one drop after the other at short but regular intervals, the moment at which coagulation begins will be found by observing the lapse of time between the reception of the drops of blood upon the glass slide and the drawing out of a filament of fibrin from a drop by the needle.

More accurate information may be obtained by means of the instruments devised by Professor Wright and by Drs. Brodie and Russell. In Wright’s method the blood coagulability is determined by aspirating
blood into a series of tubes, and by then blowing down tube after tube in succession until coagulation takes place; when of course blood can no longer be blown out of a tube. The lapse of time since the blood was shed is known as the "coagulation time." The necessary apparatus, as seen by reference to the figure, consists of a water-tin surrounded by a leather jacket lined with flannel, and constructed with a series of pockets between the layers of flannel; each pocket being just sufficiently large to admit a coagulation tube. One of the pockets is reserved for a glass thermometer comparable in diameter with the coagulation tubes in the remaining pockets.

Professor Wright's instructions are:—(a) That the capillary tubes be of equal calibre, 0·25 mm. being proposed as a standard diameter; (b) that in each tube the column of blood be of approximately equal length (5 centimetres); (c) that the blood be aspirated for some little distance up the tube to prevent its desiccation at the orifice; (d) that before filling them the tubes be warmed to blood heat by pouring water at about the normal blood temperature into the central tin; and (e) that this degree of heat be maintained as constant as possible—by further additions of hot water if necessary—until coagulation is complete. This precaution will ensure an optimum temperature, and will render uniform the results obtained during the observation or series of observations. It is desirable to allow about half a minute to elapse between the filling of successive tubes; and in ordinary cases the condition of the blood in the first tube should be tested within three or four minutes from the time of filling. If then, on testing the first tube, the blood be still liquid, a longer time must be allowed before examining the blood in the second tube. If, on the other hand, the blood in the first tube is clotted, the next one should be tested at a somewhat shorter interval after filling. The first traces of clot may be most easily detected by blowing out the contents of a tube upon a piece of white filter-paper. By this method information is obtained as to (a) the shortest time which is required for complete clotting in a coagulation tube, and (b) the longest time during which blood can remain unclotted in a coagulation tube: the mean between these results will afford a close approximation to the true coagulation time of the blood. Normal blood-clots form in these tubes in from three to five minutes.
It is obvious that, if need be, this method may be employed to investigate the action of various therapeutic agents, such as physiological styptics, on the blood.

After use the tubes are best cleansed by passing a fine brass wire through them, and then washing out with distilled water. By drawing up a little absolute alcohol any remaining water may be got rid of; and in its turn the alcohol may be removed by ether. When the last traces of ether have been volatilised, a process which may be hastened by blowing a current of air through the tubes, these are again ready for use.

Brodie and Russell’s method.—In certain respects this method possesses superior advantages, and the necessary apparatus is by no means complicated. One advantage is that a minimal quantity of blood suffices for each estimation, and that the readiness with which the instrument can be cleansed enables a number of such estimations to be carried out in a comparatively short time.

![Fig. 24.—Brodie and Russell’s coagulometer.](image)

The instrument consists of a deep air-chamber AA, closed below by a glass plate E, upon which lies a layer of water M. It is closed above by a movable glass slide G, to the centre of which is cemented an inverted truncated glass cone C. The whole is surrounded by a water-jacket WW. Inflow and outflow tubes to the water-jacket (not represented in the diagram) enable us to vary the temperature of the air-chamber at will. A metal tube T pierces the water-jacket, and to its interior is fitted a glass tube D which tapers to a fine orifice at P. This orifice lies below the lower surface of the cone C, but is directed towards it.\(^1\)

In using the apparatus the glass plate and cone are removed, and the lower surface of the latter, after thorough cleansing, is dipped carefully into the drop of blood, so that the whole of this surface, but the surface only, is wetted by the blood. This precaution ensures that the drop which is taken up shall always be approximately of the same size. The hanging drop is then brought into the air-chamber, the whole process being carried out as rapidly as possible. The instrument is next placed on the stage of the microscope, and the drop of blood observed under a low power, when, on blowing air gently through the tube D, the contained corpuscles will be set in motion, a weak and short current of air being sufficient for the purpose.

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\(^1\) The apparatus is made by Mr. A. E. Dean, jun., 73 Hatton Garden, E.C.
Observation should be confined to the edge of the drop, as the layer of blood here is thinnest, and the view of the corpuscles consequently better than in the deeper layers. It is at the free edge also that clotting is always first noted, the process gradually extending inwards at a rate which depends, to a large extent, on the surrounding temperature.

At times it is found that at the very edge of the drop the corpuscles remain quiescent, but this is exceptional. Ordinarily they move freely right up to the edge of the drop, such movement consisting in changes in their position relatively to one another, as well as in a rotation of the whole mass. On the other hand, as soon as the rim at the edge becomes solid, blowing simply causes an indentation of this rim without causing rotation of the corpuscles.

This stage it is which should be observed, as it is much more difficult to judge with any accuracy the time at which the whole drop becomes coagulated throughout.

In order to obviate any chance of fallacy as far as possible it is well to avoid unnecessary agitation of the drop of blood. We must blow very softly, and only for brief periods of time. In the following tables it will be seen that the method is capable of affording fairly concordant results in a series of observations.

The coagulation times here set out were obtained from the blood of normal individuals, the experiments being carried out in each instance at a temperature of 30° C.

\[
\begin{array}{ccc}
(1) & 3:33 & (1) \quad 3:10 \\
(2) & 3:30 & (2) \quad 3:00 \\
(3) & 3:30 & (3) \quad 3:00 \\
(4) & 4:43 & (1) \quad 3:00 \\
(2) & 4:40 & (2) \quad 3:55 \\
(3) & 4:00 & (3) \quad 3:50 \\
(4) & 4:50 & (1) \quad 3:25 \\
(2) & 3:18 & (2) \quad 3:40 \\
(3) & 3:35 & (3) \quad 3:30 \\
\end{array}
\]

The first two sets of observations were taken on successive days in the same individuals.

VII. SPECTROSCOPIC EXAMINATION OF THE BLOOD.—It will occasionally happen that information of value from the clinical point of view may be gained by means of a spectroscopic examination of the blood, which could not be easily obtained by any other method. This will be especially the case in poisoning by carbon monoxide and coal gas, or by such substances as amyl nitrite and potassium chlorate. In certain diseases also information may thus be afforded of the approaching onset of coma. I have been able to foretell the probable appearance of this dangerous complication in several cases of uremia and diabetes on finding evidence of the presence of methæmoglobin in the blood. Methæmoglobin has also been found in severe cases of cholera and leukaemia.

The discovery of haematoorphyrin has been recorded in some eventually fatal cases of sulphonal poisoning.
In suspected cases of hæmoglobinuria the diagnosis may be assisted and confirmed by spectroscopic examination of the serum obtained from a blister, which, in the event of the recent occurrence of a paroxysm of this disease, will show the absorption bands characteristic of oxyhæmoglobin due to the destruction of red corpuscles in the general circulation.

**Method of examination.**—The ordinary chemical spectroscope is practically useless in clinical work, the extent of dispersion being too great, and too large an amount of blood being required. These difficulties are obviated by making use of the micro-spectroscope for clinical examinations. Both Zeiss and Browning manufacture small instruments of admirable construction which are employed in connection with the microscope, the micro-spectroscope being substituted for the ordinary eye-piece. The fluid to be examined is placed on the microscope stage, in a tiny test-tube made by sealing one end of a short narrow piece of glass tubing, the cell thus formed being supported on a wooden foot, as at first suggested by Dr. MacMunn. This support serves also to cut off extraneous light. The upper surface of the fluid is now focussed with the ordinary eye-piece, which is then exchanged for the micro-spectroscope. If the amount of material to be examined be extremely small, the high power objective must be employed. In this way I have had no difficulty in obtaining satisfactory absorption spectra from separate crystals of hæmoglobin in a cover-glass specimen of human blood. It is advisable to use artificial light for illumination, as, if daylight be employed, confusion is apt to be caused by the presence of the Fraunhofer lines.

**The absorption spectra of hæmoglobin and its derivations.**—The normal blood-pigment hæmoglobin is capable of existing in two forms, named oxyhæmoglobin and reduced hæmoglobin respectively, which differ from one another in the amount of oxygen in combination, in the colour of their solutions, and in their absorption spectra. Oxyhæmoglobin, when examined with the spectroscope, shows two absorption bands between the D and E Fraunhofer lines, the intensity of which will depend on the degree of concentration of the pigment and on the thickness of the layer of fluid examined. Under ordinary circumstances these bands are readily visible, even in venous blood which contains a certain proportion of reduced hæmoglobin. The single absorption band, which is characteristic of this variety, and which occupies a position in the spectrum roughly midway between those of oxyhæmoglobin, is somewhat
diffused and of relatively small intensity. In order to see it clearly it is necessary to treat the blood with some reducing agent such as ammonium sulphide, by the action of which all the oxyhaemoglobin eventually becomes converted into the reduced variety.

A third modification of haemoglobin which, as previously stated, has been found in the blood during the course of certain diseases and in cases of poisoning, particularly with potassium chlorate, is named methaemoglobin. This contains precisely the same amount of oxygen as oxyhemoglobin, but differs from the latter in that its reaction is acid while the other two forms of haemoglobin are alkaline, and also in its absorption spectrum. Instead of the two bands of oxyhaemoglobin it shows four bands, of which one between the C and D Fraunhofer lines

![Chart of blood spectra. (1) Oxyhemoglobin; (2) reduced hemoglobin; (3) methaemoglobin; (4) acid hematin; (5) alkaline hematin; (6) reduced alkaline hematin.](image)

is most definite. A very similar four-banded spectrum is also presented by acid haematin (or hematin in acid solution), but the two may be distinguished by the fact that when methaemoglobin is treated with ammonium sulphide, reduced haemoglobin is produced, while treatment of acid haematin with the same reagent results in the formation of reduced alkaline haematin (see Fig. 26). The spectrum of Co-haemoglobin shows two absorption bands resembling those of oxyhaemoglobin, from which, however, they may be distinguished by their persistence on addition of ammonium sulphide.

VIII. EXAMINATION OF THE BLOOD FOR PARASITES.—This subject is fully discussed in the articles dealing with the respective diseases in which parasites of one or another kind are met with, but it may be useful
briefly to set out certain of the methods employed for their demonstration which experience has shown to be not only efficient but at the same time expeditious. Of the more highly-organised parasites met with in the blood may be mentioned the *filaria sanguinis hominis* and the *plasmodium malariae*. The ova of the *haematobium* and *Bilharzii* have been discovered in large numbers embedded in the walls of the portal vein, but they have not been found free in the blood. Both the *filaria* and the *malarial organism* can perhaps be examined best in the fresh blood, for which purpose a drop of blood should be withdrawn at such time as experience has decided to be likely to give the best results (vol. ii. p. 1065 and p. 724). A perfectly clean cover-glass is then lightly brought in contact with the drop of blood, and afterwards carefully lowered on to a glass slide, so as to produce as thin and even a film as possible. A little vaseline should be smeared round the edges of the cover-glass to prevent evaporation. To stain these organisms, extremely thin films of blood must be taken on cover-glasses and first fixed as rapidly as possible over the vapour of osmic acid, or by dipping the cover-glass in a mixture of equal parts of absolute alcohol and ether. They may then be stained in the eosin and methylene blue mixture originally devised by Canon for the demonstration of the influenza bacillus.

**Canon’s stain.**—Eosin, \( \frac{1}{4} \) or \( \frac{1}{2} \) per cent in 70 per cent alcohol, 20 parts; methylene blue, saturated aqueous solution, 40 parts; distilled water, 40 parts. Plehn recommends the addition to the staining mixture of ten to twelve drops of a 20 per cent solution of potassium hydrate. This same method will serve to demonstrate bacteria in the blood. For this purpose, however, it will be necessary, especially if cultivations are also to be made, to obtain the blood with antiseptic precautions; and it is usually better to carry out the preliminary fixing of the film by means of heat, or by treatment with a solution of corrosive sublimate. *Staphylococci*, streptococci, *pneumococci*, gonococci, and the bacilli of *anthrax*, *glanders*, *typhoid*, and *influenza* all take up the methylene blue of Canon’s or Loeffler’s stains.

**Loeffler’s alkaline methylene blue stain** consists of saturated alcoholic solution of methylene blue, 30 c.c.; caustic potash (1 in 10,000), 100 c.c. When examining for tubercle bacilli it is advisable to make use of Nielsen’s carbol-fuchsin solution. The composition of this stain is as follows:

**Nielsen’s stain.**—Saturated alcoholic solution of fuchsin, 1 part; five per cent solution of phenol in distilled water, 9 parts. The cover-glasses are floated face downwards on this solution, a little of which should previously have been heated in a watch-glass until steam begins to arise from the surface. Two minutes will probably suffice for staining. The superfluous stain is washed off rapidly, and the cover-glass is then placed in a 25 per cent solution of nitric or sulphuric acid in distilled water, until all colour has disappeared. The acid is next removed by thorough washing in water, and the cover-glass is rapidly dried by pressure between two pieces of smooth blotting-paper. If thought
desirable, the specimen may be counterstained by a few minutes’ treat-
ment with Loeffler’s solution.

For the methods of making cultivations a treatise on bacteriology
must be consulted.

As a general rule, it is only in the most severe cases that it has been
found possible to demonstrate the presence of bacteria in the blood; so
that, although such an examination often fails to afford information of
any diagnostic value, if positive evidence be obtained the prognosis will
be very unfavourable.

This rule has been insisted on by Ely, who has shown that, although
the results of bacteriological examinations of the blood have proved dis-
appointing as an aid in diagnosis, yet, by affording an explanation of com-
lications in diseases which are usually localised, they are often of value
from a pathological point of view. Thus he found pyogenic microbes
present in the blood during life in cases of pyæmic osteomyelitis, puerperal
fever, erysipelas, and infective endocarditis; the pneumococcus in pneu-
monia and infective endocarditis; the bacillus coli in cystitis complicated
with a pyæmic condition; the gonococcus in infective endocarditis after
gonorrhœa; the tubercle bacillus in tuberculosis, and the Eberth bacillus
in typhoid fever. Block has also put on record a fatal case of typhoid
fever in which the bacillus typhosus was twice obtained during life.
Kohn has obtained very similar results. He states that in cases of pro-
nounced sepsis large numbers of bacteria may be present in the blood.
He also agrees as to the grave prognosis which is indicated by the
discovery of the pneumococcus in the blood in pneumonia; a series
of negative results, on the other hand, being distinctly favourable to the
patient’s chances of recovery. Thus of nine cases of pneumonia in which
he was able to demonstrate the pneumococcus in the blood, no less than
seven were fatal; the other two being complicated with empyema and
multiple abscesses respectively. On the other hand, of twenty-three
negative cases eighteen recovered, the fatal termination in the other five
being due to various complications.

The Widal-Grünbaum method for the diagnosis of typhoid fever.

—In this method advantage is taken of the fact that on addition of a
small quantity of blood or serum obtained from a patient suffering from
typhoid fever to a dilute culture of Eberth’s bacillus, loss of motility of
the individual microbes is rapidly induced, while at the same time they
and to mass together into clumps, a process to which the term agglutina-
tion is now generally applied.

The recent researches of Grünbaum, Wyatt Johnson of Montreal, and
Durham, Wright, and others in this country, have rendered the process
more accurate and simple, and, as it is now possible to obtain the reac-
tion with a single drop of fresh or even dried blood, the method has become
readily available in clinical work. Wyatt Johnson’s modification of
Widal’s test is specially applicable to examination of the blood of patients
living at a distance. One or more drops of blood are allowed to fall on
the surface of a small piece of non-absorbent paper, which when the blood is dry can, if necessary, be sent through the post. To test for the reaction, the drop of dried blood is removed and dissolved up as far as possible in distilled water. This blood should then be mixed with varying proportions of a fresh beef-broth culture of the typhoid bacillus (12-24 hours), or with an emulsion made from a fresh agar culture, in varying proportions, the resulting dilutions of the blood thus prepared ranging from 1 in 15 to 1 in 50. It is advisable that control preparations should be made with normal blood in every instance, and all the specimens should be examined under the microscope within a definite period, preferably half an hour, after preparation.

The serum obtained from a drop or two of blood taken up into a bulbed capillary tube may be examined in the same manner, or it may be added directly to a suitable quantity of a recent broth culture.

Grünebaum's original method is as follows:—A U-shaped capillary tube is filled with a drop of blood from the patient, and the serum separated by centrifugalising. The free extremities of the tube in which the serum collects are broken off, and the serum is mixed with sixteen times the quantity of bouillon. A small quantity of fresh culture of the typhoid bacillus on agar is distributed in 1 c.c. of bouillon, and a drop of the resulting emulsion is added to a drop of the diluted serum. The mixture is then examined as a hanging-drop preparation under the microscope.

It is of importance that the reaction of the culture medium employed for the test growth of Eberth's bacillus should be distinctly acid (preferably 3.5 per cent acid to phenolphthalein in the case of peptone beef bouillon, according to Wyatt Johnson), as otherwise a scum is apt to form at the surface, or a sediment at the bottom of the culture fluid, which in either case not infrequently contains clumps of apparently dead bacilli, the presence of which would tend to obscure the reaction.

At present some doubt exists as to the exact value of the test as an aid to diagnosis, for the reason that it cannot usually be obtained until after the lapse of several days from the beginning of the disease. Again, one or two undoubted cases of typhoid fever have been recorded in which from first to last the reaction could not be obtained. On the other hand, if suitable precautions be taken, it is possible, in the great majority of cases, to demonstrate the reaction towards the end of the first week of the disease, or later. The fact that not infrequently during convalescence the test fails to afford positive evidence in cases in which it has previously been obtainable, tends to show that the specific action of the serum is not dependent on a condition of acquired immunity.

Blood-Crystals.—Under certain circumstances, concerning which as yet comparatively little is known, crystals of one kind or another may form in the blood taken from the body during the course of diseases in which the character and condition of the blood are especially affected.
Among these disorders may be mentioned certain anæmic conditions, more particularly pernicious anæmia, leukæmia, and the various forms in which septic infection may manifest itself.

1. Hæmoglobin.—It has long been known that the special blood-pigment hæmoglobin, although of proteid nature, may be obtained with comparative ease in the crystalline form from the blood of some of the lower animals, particularly the guinea-pig and the rat. On the other hand, the hæmoglobin of normal human blood is undoubtedly much more refractory in this respect, since the ordinary laboratory methods entirely fail to bring about crystallisation. Some years ago, however, I made the observation that in specimens of blood from cases of pernicious anæmia, prepared for microscopic examination, rhombic crystals of hæmoglobin not infrequently formed after the lapse of some hours. This was markedly so when the blood had been obtained from persons suffering from a severe form of the disease; especially if a certain amount of pyrexia were present, and provided that treatment with arsenic either had not been begun or had been discontinued for a time. Bond and myself have also noted the appearance of hæmoglobin crystals in blood-films obtained from cases of leukæmia; and the former observer has found that the same phenomenon can be demonstrated in cases of septicæmia and pyæmia. Human hæmoglobin invariably crystallises in the reduced condition, as may be shown by the micro-spectroscope, a point of apparent difference between the blood of man and that of the lower animals. The formation of hæmoglobin crystals in human blood, after removal from the body, is undoubtedly connected with a tendency to abnormal blood-destruction. The readiness or the reverse with which crystals appear in blood-films thus affords some measure of the effect of treatment in restraining such hæmolysis.

The method of obtaining crystals of hæmoglobin from the blood in suitable cases is simplicity itself. A fairly large drop of blood, drawn from the finger or elsewhere, is allowed to fall on the centre of a glass slide, and, when sufficient time has elapsed for the edge of the drop to have dried somewhat, a cover-glass is gently lowered upon the surface of the drop. The blood corpuscles gradually break down, and crystals of reduced hæmoglobin will become apparent, in from ten to forty-eight hours, without further preparation.

2. Hæmatoidin.—The presence of this substance, a derivative of the blood-pigment, has been detected in an amorphous form by Von Jakob in the fresh blood of a child suffering from hereditary syphilis. It is frequently found in crystalline form in old cerebral blood-clots, splenic infarctions, and blood-cysts. Occasionally these crystals, or fragments of them, are found within the substance of white corpuscles in the circulating blood under such pathological conditions as obtain in pernicious anæmia and leukæmia, during the course of which diseases minute hæmorrhages in various parts of the body are of not infrequent occurrence.

3. Charcot-Leyden crystals.—Occasionally, as in a case recorded by Ord and myself, long colourless pointed crystals have been found in
preparations of leukæmic blood. Their occurrence has not been noted in freshly-drawn blood, but crystals apparently identical with them are not infrequently to be found in the sputum, the faeces, and the seminal fluid. Comparatively little is known as yet of their chemical composition or pathological import.

Certain other methods of blood examination, of which no detailed account will be given, demand brief notice, either because they appear worthy of further investigation, although not yet rendered applicable to clinical needs, or because, although not considered of special value by myself, they nevertheless have been authoritatively recommended or somewhat extensively employed by others.

Under the first category may be mentioned the work of Graham Brown and of Huertlhe on the determination of the viscosity coefficient of the blood. These observers find that even slight alterations of the "viscosity coefficient" entail an enormous difference in the work thrown upon the heart in propelling the blood round the circulation. Dr. Graham Brown, moreover, has demonstrated the great alteration in the "viscosity coefficient" produced by a change of only a few degrees in the body temperature, the blood flowing much more readily at fever temperature than under normal conditions.

Determination of the isotonic coefficient of the red corpuscles is another method of blood examination, concerning the clinical significance of which but little is known. The "isotonic coefficient" is usually measured by the amount of NaCl which it is necessary to add to distilled water to prevent it, when added, to blood, from causing its usual destructive effect on the red corpuscles.

The quantity of salt required may, under pathological circumstances, be either greater or less than the normal amount (0.44-0.48 per cent), indicating respectively an increased or diminished power of resistance on the part of the red corpuscles.

The estimation of the number of red corpuscles in a given volume of blood, if it is to be accurate, involves no little expenditure of time and trouble. In the hope of obviating this difficulty, certain methods of indirect estimation of the corpuscular richness of the blood have been introduced. Thus, in this country Dr. George Oliver has advocated the use of a hæmocytometer devised by himself, in which the number of corpuscles is gauged by the amount of water which must be added to the blood in order to allow the passage of a ray of light through the mixture. Considerable fallacy, however, is likely to be introduced by any increase or decrease in the volumes of individual corpuscles, or by increase in the number of leucocytes, such as we find, for instance, in leukæmia.

In America the Hedin-Dalland hæmatocrit has been much used for the purpose of estimating the number of red corpuscles in the blood. This instrument is practically a small centrifuge driven by hand with the aid of a system of multiplying wheels. Each of the two arms of the instrument is arranged to hold a small tube of capillary bore, which is marked
off into a hundred equal divisions. In use these tubes (or one of them) are filled as accurately as possible with blood and fixed in place in the machine, which is then run for about a couple of minutes. The red corpuscles thus become packed together at one end of the tube. On removing the tube and placing it on a sheet of white paper, it is fairly easy to read off the number of divisions of the scale corresponding to the dense mass of corpuscles. What is really determined by means of this instrument is of course the volume of the red corpuscles, from which their number is empirically calculated, each division on the scale of the capillary tube corresponding, in the case of normal blood, to about 100,000 corpuscles. Obviously little or no reliance can be placed on estimations arrived at in this manner in the case of pathological blood; especially when, as in such diseases as pernicious anaemia and leukæmia, there is much variation in the size and shape of the corpuscles.

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REFERENCES


THE CLINICAL EXAMINATION OF THE BLOOD


CARDIAC PHYSICS

The Cardiac Valves.—1. Mechanism of the auriculo-ventricular valves.—
At each systole of the ventricles the tongue-shaped valve-flaps pendent from the margin of the auriculo-ventricular orifices are moved together toward those orifices, and meeting together across them block them. By this means the blood in each ventricle is prevented from returning into the auricle, and under the compression of the contracting ventricle is forced to make its way into the great arteries. Were it not for these valves not a drop of the blood would enter the arteries, so long as the pressure in the latter possessed a value near the normal; but for the valves its issue would be far easier back into the cavity of the auricles where the pressures are low. During diastole of the ventricle the flaps of the auriculo-ventricular valves lie in the cavity of the ventricle with their long axes convergent toward the central long axis of the ventricle. Between the valve-flaps and the inner face of the ventricular wall there is always an interval, and therefore always more or less blood (Baumgarten, Krehl). Manometric observations reveal no increase of pressure in the auricle at the moment of closure of the auriculo-ventricular valves. The discharge of its contents by the auricle into the quiescent and already partly filled ventricle somewhat stretches the slack walls of this latter, and, whether by eddy or otherwise, the valve-flaps are raised toward each other and toward the auricular opening. Then, as the contraction of the auricle passes off, the pressure in the now fully-loaded ventricle becomes higher than in the relaxing auricle. The valve-flaps thus swing together into position, and are moved to meet across the auriculo-
ventricular orifice, even before the ventricular systole has thoroughly set in. If the arterial openings of the excised heart be blocked, and through the auricles a momentary rush of water under about 12 inches pressure be allowed to play into the auriculo-ventricular orifices, the valve-flaps rise into the orifice, and come together sufficiently firmly to allow of the inversion of the heart without the escape of a drop of its contents.

The valve-flaps would be forced through the orifice back into the auricle were they not tied down to the ventricle by the chordæ tendineæ attached to almost all areas of their under surface. Each valve-flap shares in a pair of papillary muscles; these latter are so placed in regard to the valve-flaps that the resultant of their combined individual directions of pull lies strictly along the long axis of the ventricular chamber, and at right angles to the plane of the auriculo-ventricular orifice itself (Ludwig).

The auricular face of each valve-flap in its position of closure is convex. The thin contiguous edges of the adjacent valve-flaps are bent abruptly downward, side by side, tightly apposed; the tenuous edges of the membranes bear, therefore, no part of the great strain to which the valve elsewhere is subjected; for these edges, projecting into the ventricular cavity, are supported on both sides by the fluid pressure of the blood in the ventricle. That this is the position of these parts of the valve is proved by the following among other considerations: the chordæ tendineæ which are inserted near the free margin of each valve-flap are much shorter than those inserted into the midrib of the flap.

Regarding the use of the papillary muscles, it has been shown (Roy and Adami) that the papillary muscles begin to contract later than does the rest of the ventricle; as the ventricle shortens from base to apex during systole, the papillary muscles, if they are to afford the chordæ tendineæ a suitably placed support, and to prevent retroversion of the valve-flaps into the auricle, must shorten in order to maintain their distance from the auricular orifice.

It has been suggested (Porter) that the auriculo-ventricular valve-flaps and their papillary muscles aid the filling of the auricles with blood. A considerable negative pressure arises in the auricle during the earlier part of the ventricular systole; this seems to occur at the time of contraction of the papillary muscles, and to be due to their drawing down and flattening the valvular curtains which form so large a part of the floor of the auricles. If so, the auricular cavity would be enlarged, and blood drawn into it from the great veins.

It must not be forgotten that an important detail in the mechanism of the closure of the auriculo-ventricular orifices is the circularly arranged muscle surrounding those orifices, as a true sphincter. This sphincter appears to be important, especially for the tricuspid orifice. In the heart of the bird the tricuspid orifice is unprovided with valve-flaps, and its closure is effected wholly by a muscular sphincter.

2. Mechanism of the semilunar valves.—So long as the pressure in the ventricle is below the pressure in the great arterial trunk leading from it,
so long will the semilunar valve-flaps meet across the arterial ostium and occlude it. When examined under a pressure approximately that of the aorta, the valve-flaps are seen to lie apposed across the orifice; if one of the flaps be displaced gently towards its attached border, the other two cusps follow it, becoming correspondingly more stretched. The cusps, therefore, in the closed position of the valve mutually support one another. When during the systole of the ventricle the intraventricular pressure becomes higher than the aortic (resp. pulmonary) the valve-flaps yield, are moved apart, and leave between them a triangular opening.

When the valve is open, the position of the cusps is with their free edge convex toward the arterial wall, but the cusp membrane does not lie apposed to or quite close against the wall. In the open position of the valve the arc formed by the curved wall of the sinus of Valsalva may be said to have its chord approximately represented by the free edge of the cusp. The supposition of Brücke that the cusps when the aortic valve is open are pressed back against the aortic wall, so as to block the entrances to the coronary arteries, is completely disproved.

The closure of the valves seems to be brought about in the following way:—During systole the cavity of the ventricle, where it adjoins the aortic opening, is narrowed by the bulging into it of the contracted muscular wall; it forms, in fact, a narrow channel which ends in the direction of the aorta in the triangular cleft between the semilunar cusps in the wide root of the aorta with its triple circumferential bays—the sinuses of Valsalva. At the place where the narrow stream suddenly embouches into the wide aortic channel eddies are formed, curving back behind the valve-cusps, and constantly tending to bring these together. The cusps are, however, kept apart by the pressure of the blood flowing between them; as soon, however, as that flow ceases the cusps rush together, as if were under the force of a spring. Ceradini’s account of the eddies which come into play on closing the valves is as follows:—If in a vertical tube containing water, in which visible particles are suspended, a piston at the lower end of the tube be pushed upward, the water in the axis of the tube is seen to move with nearly twice the velocity average for the whole column; along the face of the wall of the tube the water moves so slowly that the piston overtakes the particles suspended in it. As this occurs the particles are seen to be swept from the circumferential zone by a centripetal current conveying them into the axial stream. Along this they rush upward to the free surface of the fluid, where they sweep outward in a centrifugal eddy to reach the wall of the tube again, there later once more to be overtaken by the piston and swept inwards in a centripetal eddy (inversion). If the ascent of the piston be suddenly checked, the above currents in the fluid are modified to the extent that an actual back flow sets in downward along the inner face of the tube. The result is that at the moment the piston stops, the column of water above it is split into two parts—into an axial cylinder moving forwards and a peripheral layer moving back—
wards, the two being connected above by a centrifugal eddy, below by a centripetal (inversion) eddy. To this latter is due the bringing together into position the cusps closing the aortic opening. The cusps thus brought together are held so by a mechanical force measurable in the left heart by the product of the difference between the aortic and ventricular pressures into the area of the valve-flap, excluding their margins. It is probable that the cusps are partly supported under this strain by the thick bulging myocardium of the ventricular wall on which they may partly rest.

The cardiac sounds.—In 1810 Wollaston showed that skeletal muscle, when it contracts under the will, emits a sound—the muscle-note. The British Association Committee in 1836 declared the first cardiac sound to be the muscle-note of the ventricles, but their observations were not decisive. Ludwig, in 1868, succeeded in proving clearly that when the heart is so placed as to convey by its mass-movement no shock to any vibrator, and at the same time is so inadequately filled as to exclude the possibility of tension of any of its valve-flaps, the first cardiac sound continues to be distinct.

But it has been shown (Wintrich) by means of resonators that the normal heart-sound consists of two notes, the lower of which only can be considered a muscle-tone. The higher is due to the vibration of the auriculo-ventricular cusps and the column of blood they support. This seems clear from the fact that it can be heard if these valve-flaps are suddenly rendered tight in the dissected heart. The first sound of the heart is therefore found to be due to the vibration of (a) the muscular wall of the ventricles, (β) the auriculo-ventricular valves, and (γ) the mass of blood in the ventricles.

The second cardiac sound has been traced to sudden tightening and subsequent vibration of the semilunar valve-flaps. The vibration of the columns of blood in the aorta and pulmonary artery is also partly answerable for the sound. If the root of the aorta and its valve be cut out and tied to the lower end of a vertical tube filled with blood, and the valve be then rendered slack by gently pushing it up from below, and be then suddenly rendered tense by removing the support from under it, a sound is produced. If next the length of the tube and column of blood be doubled, and the experiment repeated, the sound is lowered in pitch although the tightness of the valve-flap is increased. Hence the resonance of the tube and column of blood rather than that of the valve-membrane is the predominant factor in the sound (Talma). But analysis proves the sound to be compounded of a lower note due to the vibration of the column of blood and a higher note due to the vibration of the valve-membrane. The sudden tightening of the valve-flaps and the production of the second sound occur not at the closure of the semilunar valve-flaps, but quickly after.

Of the sounds emitted from the heart the weakest to hear on the surface of the body is that of the right ventricle; the loudest that of the
left ventricle. The aortic sound is usually not so loud as that of the pulmonary artery (Vierordt).

Mass movements of the heart.—The diminution in volume undergone by the heart as its ventricles expel their content of blood is accompanied by a change in its form. If the diameters of the heart in situ be measured in the opened chest of a supine animal, it is found that during systole the side to side diameter diminishes much—more than the front to back. This is, in systole the heart becomes more or less ellipsoidal in cross-section. Probably in the unopened chest and in the erect position its cross-section in diastole as well as in systole is nearly circular. In systole the ventricles are somewhat shortened; but the apex shifts little; it is the base which moves, descending and coming forward towards the apex. This movement of the base is accompanied by a lengthening of the aorta and pulmonary arteries. The latter causes descent of the base of the contracting ventricles, and the descent compensates the shortening of the ventricles, and retains the apex in contact with the chest wall. The cardiac impulse is a protrusion of the chest wall over the surface of the ventricles at the moment just before the expansion of the artery at the wrist. As the ventricles suddenly become hard their long axis becomes more horizontal to the vertical plane of the chest, and is tilted against the resistance of the chest wall. Around the spot where the soft parts of the chest are protruded by the impulse they are found slightly drawn in at the time of each systole. This “negative impulse” is caused by the shrinkage of heart in the air-tight chest as it empties itself, being followed inward by the lungs and to a small extent by the soft parts of the chest wall under the pressure of the atmosphere.

Graphic records of the cardiac impulse can be obtained by one or other of the different forms of cardiographs. Cardiograms, however, in spite of much attention bestowed on their elucidation, still remain unsatisfactory, on account of their variability and the difficulty of disentangling their component factors.

The filling of the heart.—The factors concerned in the filling of the heart are many. The acceleration imparted by the ventricles to the blood, both mediatly through the elasticity of the arterial wall and immediately in the heart, gives the momentum of the inflowing blood. Then there is the excess of static pressure in the great veins over that in the diastolic auricle and ventricle. Contributory is the aspiration by the thorax during the act of inspiring, and also the slighter thoracic aspiration produced by the diminution in volume of the heart itself at each systole. The circulatory effect of the rhythmic decrease in intra-thoracic pressure due to these two causes is illustrated by the pulsatile recession of the brain in the cranial fontanelles. Finally the ventricles and the auricles during their relaxation period generate within themselves pressures lower than the pressure in the veins.

Intra-auricular pressures.—The curve of intra-auricular pressure
during the cardiac cycle, when its examination is begun at the outset of the auricular systole, shows—(i.) a systolic rise of pressure, which is synchronous with the period of contraction of the auricle; (ii.) a first diastolic fall of short duration corresponding with the relaxation of the auricle and with the earliest part of the systolic rise of intra-ventricular pressure. It is noteworthy that the closure of the auriculo-ventricular valves causes not even a transient elevation of pressure in the auricle. (iii.) The first diastolic rise of pressure is short, and occurs during the early continuance of the ventricular systole. It may be due to the bulging up of the partition between the auricle and ventricle under the high pressure in the latter. It is absent when by vagus inhibition the ventricle is prevented from beating. (iv.) A second diastolic fall occurs while the intra-ventricular pressure is still rising. It lasts longer than the former fall, and is more marked. Its cause may be in the pulling down of the auriculo-ventricular valve-flaps by the contraction of the papillary muscles, which, as Roy and Adami proved, contract somewhat later than the myocardium elsewhere. (v.) A second diastolic rise occurs as a steady increase of pressure, which continues until the beginning of the diastole of the ventricle. (vi.) The third diastolic fall, best marked when the heart is beating slowly, is due probably to a low pressure generated in the common cavity of auricle-ventricle by the suction of the relaxing ventricle. In a particular case the values of the pressures were in the dog's heart systolic rise 9 mm. Hg.: 5, -10, 5, 5. The flow from the veins into the auricle is intermittent, ceasing during the systolic and the first diastolic rise.

The filling of the ventricle.—As the systole of the ventricle ends and relaxation of its muscle occurs, a negative pressure is generated in the ventricle. Moens supposed that in the latter part of systole the ventricle developed in itself a negative pressure, but his hypothesis is unsupported by subsequent physiological observations. The negative pressure is at first considerable, but this degree of it lasts for a very short time only (Porter), and is over before the auriculo-ventricular valve-flaps can open; it does not, therefore, help directly to fill the heart. There succeeds a longer period of much slighter negative pressure; this assists, the auriculo-ventricular valves being open, to draw blood into the ventricle from the auricle, and into the latter from the veins. Its importance for the filling of the heart is proportional to its duration.

The intra-ventricular pressure.—The rise of pressure in the ventricle which accompanies the systolic contraction of its muscle proceeds gradually though rapidly. It closes the auriculo-ventricular valves almost at once, but for some \( \frac{1}{3} \) of a second, though steadily increasing, it cannot burst open the semilunar valves. This is the period of "getting up pressure," the "prophygmic interval" as Allbutt terms it. The pressure reaches its maximum in about \( \frac{1}{2} \) of a second, and for more than the latter half of this interval the semilunar valves have been opened. The pressure continues to rise, therefore, after the opening of those valves has been effected; nor does it recede far from the maximum until the relaxation of
the muscle sets in, about \(\frac{2}{10}\) of a second after the opening of the valves. The pressure in the ventricle then drops below the pressure in the aorta, and the semilunar valves close. If the pressure in the arterial system is high, the pressure in the ventricle runs a course somewhat different from the above, for instead of reaching its maximum soon after the opening of the semilunar valves it slowly increases throughout the systole, becoming maximal immediately prior to relaxation (Huertthle). In both cases, however, the curve of intra-ventricular pressure is a relatively flat-topped one, showing a "systolic plateau." As Professor Allbutt wisely says, "It is the function of a healthy heart and arteries to promote the maximum of blood displacement with the minimum alteration of pressures." In the systolic plateau two minor undulations of pressure are seen; the causation of these, which are synchronous with two seen in the aortic pressure-pulse, is not clear. On the setting in of relaxation of the ventricle the pressure, in \(\frac{1}{10}\) of a second, falls from between 150 and 180 mm. Hg. to below zero; and then for \(\frac{1}{60}\) to \(\frac{1}{10}\) remains negative. The negative pressure generated varies much in amount, but may reach nearly 20 mm. of Hg. Gradually the pressure rises to a little above zero, and remains a few millimetres above zero throughout the rest of the diastole, until the auricular systole occurs and drives it slightly up to about 10 mm. of Hg.

| Systole of ventricle before the opening of the semilunar valves, | 0.03 |
| Continued contraction of the ventricle and escape of blood into aorta | 0.27 |
| Total systole of the ventricle | 0.3 |
| Diastole of both auricle and ventricle, neither contracting passive interval | 0.4 |
| Systole of auricle (about or less than) | 0.1 |
| Diastole of ventricle, including relaxation and filling, up to the beginning of the ventricular systole | 0.5 |
| Total cardiac cycle | 0.8 |

It is important to note that with a frequent pulse the frequency is obtained without appreciable shortening of the cardiac systole, and almost entirely by reduction of the resting period of the heart, the diastole. Further, with a high arterial pressure the period of complete ventricular relaxation is somewhat shortened.

**The work of the heart.**—The heart is a machine which converts chemical energy into heat, electrical difference, and mechanical work. Only, the last-named form of its output of energy need be considered here. During \(\frac{1}{3}\) sec. of the ventricular systole the left ventricle exercises a pressure on its contents often amounting to close on 200 mm. Hg.; that is, a pressure of 272 grammes on each square centimetre of its internal surface; 100 cubic centimetres is a low estimate of the output of blood.

By Torricelli’s theorem, the velocity \(v\) of a fluid streaming through an opening in the floor of a vessel under fluid pressure \(H\) is \(v = \sqrt{2gH}\),
where \( g \) is the acceleration of gravitation (9.8 metres). The kinetic energy \( E \) of this fluid is, if \( m \) is the mass of the fluid, \( mgH \). And \( mg = w \), the weight of the fluid, so that \( E = wh \). In other words, a drop of the fluid starting from an orifice in the vessel will have at that orifice the same velocity as if it had fallen freely from the level of the top of the fluid; and the kinetic energy can be measured by the work required to raise it again to a height equal to the height of the top of the fluid in the vessel. If the ventricle be assumed to have no external resistance to overcome in expelling the blood, its work \( W \) would be \((V \text{ being the velocity which the blood would have under a fluid pressure corresponding to the pressure exerted by the ventricle}) \frac{mV^2}{2} \). But the ventricle in expelling its blood has to do so against a high resistance: only a portion of its energy is employed in imparting velocity to the blood. The total pressure is divisible into two parts, I. and II.,—I. spent in overcoming resistance in the tubing of the blood-vessels, II. the flow-producing pressure or velocity pressure. The mean velocity can be ascertained by experiment; its value per second is

\[
\text{Volume of outflow} \times \text{time (seconds)} - \text{Q} \times \pi r^2 h, \text{ and } II = \frac{V^2}{2y}.
\]

The portion of the work of the heart which is used in overcoming the resistance is the difference between the whole work and that quantity arrived at above for II. This latter amounts to about 1.28 grammes. If the velocity of the blood in the aorta be taken at 5 metre per second, and the quantity ejected from the ventricle at 100 c.c., and the pressure in the aorta to average 150 mm. Hg., we have the work of the left ventricle amounting to 204 grammes done against external resistance + 1.28 grammes represented by the momentum of the moving blood: a total of 205.28 grammes. The work done by the right ventricle against external resistance may be taken at about 81.6 grammes. The energy of the muscular contraction directly expended in imparting velocity to the blood is quite small in comparison with the amount expended in distending the arterial wall. The arterial wall, and especially the aorta, is to the heart as a high-pressure cistern to the pumping-station that replenishes it, as its air-chamber to the fire-engine, or as the bag to the bagpipes (p. 476). And probably 100 times more of the heart's work in moving the blood is expended on it indirectly through the aortic arterial cistern than directly on the blood itself. The potential energy entering the heart in chemical form is transmuted to the potential mechanical energy of the heart wall, then to the kinetic energy of accelerated material, and again to the mechanical potential energy of the blood-vessel walls, ultimately to be converted into heat. In the tensions and relaxations of the arterial walls, and in the friction of the moving blood, the heart's energy is continually being converted into heat. In this form the contractions of the heart yield about \( \frac{1}{6} \)th of the total
daily heat production. With a pulse frequency of 72 per minute the
work produced by the heart is nearly 25,000 metre kilogrammes in the
24 hours—work more than equal to lifting itself six times in the 24
hours from the sea-level to the summit of Mount Everest.

Experimental observation shows that the heart is a machine which
maintains under varying circumstances—so long as its nervous system
and its own nutrition are not interfered with—a curiously constant
action in two respects; namely, in the duration of the ventricular systole
and in the quantity of the output of blood into the aorta. To keep
these constant the heart has under varying circumstances to perform
very various amounts of work. When the aortic pressure is high, it is
found by direct measurement that not only is the maximal pressure
produced in the ventricle at each systole much higher than when the
aortic pressure is low, but also that the average pressure in the ventricle
during systole is much higher than when the heart is beating against a
low aortic pressure. The systolic pressure-plateau is much heightened.
High arterial blood-pressure involves, therefore, a greater expenditure of
energy by the heart at each systole. It is interesting to note that a rise
of arterial pressure is in most cases followed by a reduction of the frequency
of the heart's rhythm. This is in consequence of excitation of the vagus
centre; the stimulation being in part a reflex started from the wall of the
heart itself, and in part a direct effect of the high pressure of the blood
circulating in the brain. An important factor determining the work of
the heart is the distension of the ventricular cavity in diastole. The
pressure on a unit of surface of the cavity remaining the same, the total
intra-ventricular pressure will vary approximately as the square of the
radius of the cavity if the cavity be taken as approximately spherical.
Thus Roy and Adami have pointed out that distension of the
ventricle means not only increase of the tension of the muscular fibres,
but also increase of the lateral pressure on their surface in propor-
tion as the square of their increase in length. But, as they further
pointed out, the content of the cavity increases as the cube, and the
muscle fibres in order to expel the same constant quantity of blood from
the dilated as from the undilated ventricle need to shorten to a relatively
less extent than was required of them before. The effect of diastolic
distension is therefore, if the output from the ventricle at each systole
remain the same, to leave a larger residuum of blood in the ventricle at
the end of systole. Recent investigations (Roy and Adami, Huetherle)
have shown that to suppose that the ventricle empties itself completely at
each systole is erroneous. Not only does it not do so, but the residual
quantity of blood varies a good deal, and with it varies generally the
amount of distension of the ventricle in diastole. The amount of disten-
sion of the ventricle, in other words, the degree of stretch in the muscle-
fibres, at the moment when they enter into contraction, is an important
determinant of the force of their contraction. All muscles respond by
greater contraction when stretched than when unstretched. This increase
in contraction is seen chiefly in increase of the work done, and the amount
of actual shortening of the muscle is usually less when it is placed under considerable stretch than when it is not. The work done (lift \times load) and the heat given out, are, however, greater. The ventricle when well loaded, or even excessively loaded, may from our general knowledge of the effect of tension on all muscular structures be expected to expend more energy and do more work at each contraction than when lightly loaded. But it does not necessarily follow that a largely distended ventricle is during diastole more loaded, that is, under higher tension than one only normally distended. The tonus of the heart-muscle is variable, and its tension will depend on the tonus. Moreover, the heart may be considered an after-loaded muscle, its load only coming into play during its contraction. The amount of blood expelled at each systole will be increased in a largely distended ventricle, and is found by experiment to be increased; but at the same time the nervous system is likely to be excited to reduce the frequency of repetition of the heart's beat, and in that way to spare the expenditure of energy by the muscle-cells.

The diastolic size of the ventricle also influences the contraction of the ventricle in another way. The mechanical condition of the contraction of the ventricular muscle differs in one respect remarkably from the conditions obtaining in the skeletal muscles: in the skeletal muscle the contractions are in the execution of most movements approximately isotonic; that is, while the length of the muscle alters, its tension remains approximately constant; broadly taken, it is only in using the muscles for fixation that the contraction becomes isometric, that is, without change in length. The contraction of the heart during the time of getting up pressure is, on the contrary, practically isometric. The muscle-fibres can only alter their length so far as the cavity of the ventricle can be altered in its shape, its volume remaining constant. But the larger the chamber of the ventricle the smaller the amount of shortening, which, as explained above (Roy and Adami), is necessary for reducing the size of the chamber by a given volume. The output of the heart remains fairly constant for each systole. The amount of systolic shortening of the cardiac fibres then is less when the diastolic ventricle is largely distended than when it is little distended. The contraction in the former case approximates nearer to the isometric condition than in the latter.

In many morbid conditions increased work is thrown upon the heart. In mitral and in aortic regurgitation the ventricle is not an “after-loaded” muscle to the extent it normally should be; its load in those cases is applied in diastole owing to the excessive filling of the heart by backflow. Similar increased diastolic volume of the heart may be brought about by compressing the abdomen and the veins therein (Roy and Adami). As stated above, a certain amount of diastolic loading is favourable to the heart's contraction. In aortic stenosis an extra load is imposed on the ventricle at each systole. The heart is more than normally after-loaded; and here again high-tension of the muscle is, within limits, a favourable condition for output of energy by the heart. But tension beyond a certain degree, and applied for more than a short period, is harmful here as in the
case of other muscles. The heart, as Rhy and Cohnheim have so well insisted, offers remarkable examples of the reserve power characteristic of the mechanisms of the animal body. By artificially reducing the lumen of the aorta even greatly, the aortic blood-pressure is but little lowered; it is maintained by the expenditure of perhaps a fourfold amount of work by the ventricle, as has been proved by manometric measurements. And furthermore increased activity within limits in the cardiac muscle leads, as in other muscles, to growth and further development of the muscle. To a certain extent, therefore, the heart possesses not merely a great temporary reserve power, but in virtue of its reaction of "hypertrophy" a high degree of permanent reserve power.

The peripheral resistance to the heart.—Our knowledge of the conditions of resistance offered in the circulation of the blood to the action of the heart can be satisfactorily dealt with from a physical point of view only by use of laws which connect together certain measurable facts concerning the blood-vessels and the blood. We require to know the amount of motive force which, as shown above, may be taken to be the aortic blood-pressure, the velocity of flow of blood, and the resistance which is overcome by the streaming blood. The last-named—the resistance—is composed of two factors, the one resident in the dimensions of the channel, the other in the properties of the fluid—the blood.

It has just been said that of the factor resident in the properties of the vascular channel the dimensions only are of account. The resistance which the channel offers to the flow of fluid along it diminishes with the shortness of the tube and with the increase of the bore of it. The nature of the material composing the tube is practically without influence on the flow. A tube of given dimensions offers the same resistance to a stream of water within it whether it be of metal, of glass, or of any other material. Every moving fluid streams along in a channel lined by its own fluid particles, and the layer of fluid immediately next the wall of the containing channel is practically at rest.

The factor depending on the properties of the blood itself is measurable in terms of standard fluids, and is due to what is called viscosity, its internal friction. Fluid flowing along a channel may, of course, be considered as though composed of a number of concentric fluid cylinders ranged round an axial thread of quickest stream, and contained within an outermost sheet where velocity is reduced to zero. In their streaming motion, therefore, the particles of the fluid move over and among their fellows, and this relative movement is opposed in the fluid by its specific coherence or viscosity. As to its degree, this internal resistance is largely influenced in one and the same fluid by temperature. Dr. Graham Brown has proved experimentally that the blood flows with considerably less resistance along tubes when warmed to fever heat than it does at normal body temperature. The internal friction of distilled water is decreased 250 per cent by raising its temperature to blood-heat as compared with its internal friction at 0.5° centigrade.
Between the dimensions of a channel, the pressure-head feeding it with fluid, and the quantity of fluid output from it, certain laws of relation are known. Poiseuille’s “law” discovers the amount of fluid escaping from any tubular channel of known dimensions fed under a known pressure-head. The output \( Q \) in unit time varies, when the length of the tube is very great in comparison with its diameter, directly with the fourth power of the diameter \( d \) of the tube, and with the feed-pressure \( h \); and inversely with the length \( l \) of the tube.

\[
Q = \frac{d^4h}{l}.
\]

From this, by comparing outputs of various fluids with output of a standard fluid (distilled water), the coefficient of internal friction \( c \) can be obtained; so that

\[
Q = c \frac{d^4h}{l}.
\]

Poiseuille’s law is in all hydrodynamics perhaps the nearest approach to accord between theory and practice. It is, however, formulated for conditions which are not very approximately those existing in the circulation of the blood. It deals with flow along cylindrical tubes under constant pressure. The blood-vessels are but approximately cylindrical, and we shall probably never be able to ascertain their particular dimensions from moment to moment, as, under the influence of the nervous system, we know they must be continually changing. Again, they are curved and complexly branched; furthermore, the pressure in the blood-channels is to a large extent a pulsatile one. The last difficulty has been especially investigated by Huertthie. He finds that, in experiments carried out with distilled water, a pulsatile pressure resembling that in the arteries did not seriously upset the Poiseuille law so long as it could be accurately averaged. The results obtained under the pulsatile pressure harmonised well with results obtained under an equal average but constant pressure. A further difficulty lies in the blood being not purely fluid, but a fluid containing semi-solid bodies suspended in it. The inspissation of the blood, which constantly occurs as an element of “collapse,” in acute cholera, and so forth, probably alters greatly the viscosity coefficient of the circulating blood.

These circumstances complicate the application of Poiseuille’s law to physiology. It is, however, possible for a given brief period to ascertain certain data which are of use in forming a conception of the amount of physical resistance which the heart overcomes in maintaining the circulation. We can determine the fluid pressure in a vessel, the amount of blood flowing through that vessel, and the viscosity coefficient of the blood of the animal at the time and at its normal temperature, also in some cases the diameter and length of the channel. Huertthie has recently determined the viscosity coefficient. He allowed the blood to flow direct from the carotid through a calibrated tube, and measured
contemporaneously the outflow from the tube and the pressure-head feeding the tube with blood. The blood was successfully prevented from cooling, and all fear of interference from clotting was avoided by reducing the period of flow to less than thirty seconds. The time was measured in hundredths of a second, the quantity of outflow in cubic millimetres. In this way the following results were arrived at:—

(i.) The coefficient of viscosity of the blood is in one and the same species of animal relatively constant.

(ii.) In one and the same individual animal the viscosity of the blood when measured by observations with tubes of various size and with various heights of arterial pressure is found to give an almost exactly identical coefficient. From this it would seem that the suspension of the corpuscles in the blood does not seriously affect the application of Poiseuille's law to it as a fluid.

(iii.) The average coefficients of viscosity for the blood of different species examined were found to be, compared with water at 37° C. as 1, as follows:—Blood of dog, 4·5; of cat, 4·1; of rabbit, 3·2. Of these, that of the dog probably most closely approaches that of man.

With the data of pressure-head, quantity of outflow, and viscosity coefficient found, there remain in Poiseuille's formula only two unknown quantities, namely, \( d \) the diameter and \( l \) the length of the cylindrical tube-channel. If \( d \) be represented by a definite number, as in certain cases it can be, then we can solve the equation, in so far that we can determine the length of a tube through which the same quantity of blood would flow in unit time—as through the aorta—and in that way obtain a definite expression of the amount of resistance in the circulation along the aorta.

Huerthle finds in this way that the aortic channel of the rabbit offers to the blood-flow a resistance equal to that which would be offered by a cylindrical tube of the same diameter as the aorta and 300 m. in length. Again, making use of data \( h \), the arterial pressure, and \( Q \) the quantity of outflow of blood from the renal artery, and \( d \) the diameter of the renal artery under a pressure of 100 mm. Hg., Huerthle found the resistance offered in the vascular path through one kidney. The resistance offered by one kidney (dog) weighing 100 grams is equal to that which would be offered by a tube of the same diameter as the renal artery (of the dog), namely, 4·6 mm., and having a length of 35 metres. Under the influence of diuretics this resistance becomes greatly lessened, so as to correspond with a tube of similar diameter, but only 22 metres in length.

One very remarkable conclusion from the above is that the resistances offered in the aortic channel and in the renal respectively are so greatly different as probably to indicate a profound difference in function. In comparing the resistances offered in the two channels, we can express both in tube-lengths of 30 m.; but then the diameter of the aorta must be reduced in the tube that represents it to 4·5 mm. That is, in other words, the aorta has a relatively greater diameter than the renal artery. This leads to the conclusion long ago introduced by E. H. Weber, that the
aorta, with its peculiarly elastic wall, is not merely a channel, but a distensible reservoir for the blood thrown out by the heart; it stores up this blood temporarily for distribution during diastole (p. 471).

In using Poiseuille's law it must be remembered that it cannot be applied directly to solve the relation between speed of blood-stream and height of blood-pressure in the animal body, although this is sometimes done. Inasmuch as the vascular channels are extensible, and their diameter therefore variable under alteration of blood-pressure, the relationships that hold good between pressure and velocity in rigid tubes will only obtain in modified degrees. The innervation remaining unaltered, we may assume that to raise the pressure twofold in a distensible tube will more than double the velocity.

But the main portion of the work of the heart is expended immediately, not on moving the blood through the vessels, but in stretching the arterial wall. The elasticity of this wall is therefore of importance in physical action of the heart. Wertheim and Roy examined the elasticity of the aorta by hanging weights on a strip of uniform cross-sectional area taken from it. Roy, by an ingenious apparatus, obtained continuous graphic records while the load was uniformly increased in weight, and thus obtained curves in which the weights are represented by the abscissae, the elongations constituting the ordinates. Both he and Wertheim agree that the curve obtained (if the strip be fresh and from a healthy vessel) is an hyperbola. Roy and Zwaardemaker have further examined experimentally the increment of cubic content of the vessel obtained under heightened pressure. Starting from a pressure about equal to that normal in the blood-vessel under examination, they found that, under successive equal increments of pressure, the increase obtained in capacity is greatest at first; and as the pressure is gradually heightened, the increase in capacity obtained becomes less and less. They found also that as the pressure starting from normal (for example, 120 mm. of mercury for the carotid of the cat) is reduced by successive equal decrements, the diminution of capacity follows more rapidly at first than later. These observers, therefore, find the extensibility at its greatest at a range of pressures which are frequent and usual in the vessel under examination. Also that above those pressures the curve of extensibility is hyperbolic. It is clear, therefore, that with a high arterial blood-pressure a certain further absolute increase of pressure will distend the vessel less than will the same absolute increase of pressure under a lower arterial pressure. Also that the injection by the heart into the aorta of a certain absolute quantity of blood will raise the arterial tension relatively more when the pressure is already high than when it is about the mean or is low. The walls of the smaller vessels have been proved to be more easily distensible than those of the large, so that any increase in the amount of blood in the arterial system will locally distribute that blood in the smaller or larger vessels relatively differently under low than under high arterial pressures.

It is noteworthy that the rupturing strains of the arteries is proved
by experiment to be about twenty times greater than any strain the body can put upon them; this is true, of course, of healthy vessels.

**Influence of the force of gravity on the heart.**—It might at first sight appear that since the blood in circulation lies practically in a vertical circuit, the effect of gravity as regards the work to be done by the heart in maintaining the movement of the blood would not be affected by gravity, the weights of the blood in the up-stream and down-stream columns balancing one another. But such a view leaves out of consideration the effect of the static pressure of the fluid columns in the vessels in stretching the walls of the vessels. L. Hill has recently investigated the results of this for the heart and the circulation generally. In respect of the former he points out that the force of gravity must be regarded as a cardinal factor in circulatory problems. The splanchnic vaso-motor system is far more developed in upright animals, such as the monkey, than in rabbits and dogs; and therefore is probably very complete in man. He proves that when the power of compensation is damaged by paralysis of the splanchnic vaso-constrictors, for instance by shock, in asphyxia, or by chloroform, the blood drains into the abdominal veins, the tonus of the splanchnic vessels not being sufficient to resist the hydrostatic pressure if the upright position be assumed; in consequence the heart empties and the cerebral circulation ceases. In the horizontal and in the "feet-up" position syncope is avoided or recovered from, the force of gravity acting in the same sense as the heart. To bandage the abdomen firmly has the same restorative effect. Chloroform by destroying the compensation for gravity in the circulation can kill an animal if the posture be one in which the abdomen is on a lower level than the heart.

C. S. Sherrington.

**REFERENCES**

CHLOROSIS

SYN.—Latin, Morbus virgineus (Lange, A.D. 1520); German, Bleichsucht; French, Pales couleurs; English, Green-sickness.

[Professor Stockman tells the author that the name Chlorosis was given to this disease by Jean Vavandali in A.D. 1620.]

Introductory.—ANÆMIA.—That in the course of many diseases the blood should vary in composition, chiefly in the direction of impoverishment, is to be expected. It may thus vary in more than one quality; it may vary in mass; in plasmatic value; and in corpuscular value. In pining, for example, we note loss of water, loss of plasma, and loss of red corpuscles; as proteids fail, the water, which is retained more or less loosely by them, tends to escape; finally, the corpuscles lose their vigour and the activity of their growth. We have no means of measuring the fluctuations of the mass of the blood with any approach to accuracy; still it seems certain that the blood does vary in mass; sometimes in the direction of excess, more frequently in that of defect. Smallness of arterial pulse is no guide in this matter; the artery, under observation may contract upon its contents so as to produce a relative anaemia of
a particular area; or a general arterial anaemia may coexist with a venous plethora, the mass of the blood not being diminished. It would seem, however, that in some diseases, such as cancer or exhausting discharges, and in old age, the mass of the blood is diminished; the arteries are unfilled, and there may be no sign of venous distension in any area. It seems probable also that in the anaemia of young men the mass of the blood decreases; in chlorosis it does not fall, and is supposed even to rise (Rubenstein and James).

Of the variations in the composition of the plasma and in corpusculation we have better evidence as, by methods described in a previous article (p. 408), we are enabled to submit these constituents to direct estimation. In the present article we have no concern with excessive values, our text is poverty of the blood. Moreover, seeing that anaemia is a factor in many diseases, I must refer the reader to other articles of this work—as to those on pernicious anaemia, splenic anaemia, leukæmia, wherein the blood changes are eminent; or to phthisis pulmonalis, chronic dyspepsia or diarrhoea, wherein the anaemia is rather a secondary event—in which certain deteriorations of the nutritive fluid are particularly described. We have some concern here, however, with anaemia occurring in the course of temporary deviations from health as distinguished from that of maladies in which the defects of the blood are of a secondary kind. Apart from the graver maladies we are all of us familiar with states of debility and lack of colour and condition which, at whatsoever time of life they may come on, we attribute, and often with reason, to a temporary and curable impoverishment of the blood. There are certain times of life when we may be too ready to put down any such flagging of sanguification to transient causes, as for instance in boys and girls in whom the demands of growth and development are extraordinary; there are other times of life, as for instance in advancing years, when we are on the alert to see in the change a herald of organic disease, and may be happily deceived nevertheless, for old persons too are occasionally prone to fail in the common task of keeping the blood up to its proper standard; though in them this failure is always of more serious meaning than it is in the young. Again, the blood may be sufficient in mass, and yet deficient either in nutritive value, or in oxidising power; or indeed in both these qualities together. For these various states sundry and somewhat uncouth names have been provided, such as hypalbuminosis, oligocythaemia, and so on; while defect in the mass of the blood has been named oligæmia—names not without their convenience. We also hear of hydræmia as the name for a state of the blood in which the fluid is said to be unduly diluted with water, and thus, if not diminished in actual bulk, defective in proteid matter. It is said that the blood of anaemic young men is not deficient in hæmoglobin, and that they are not very pallid; that it is the quantity of arterial blood, or at any rate of the plasma, in the vessels which is under the standard: the blood does not spring from the finger when pricked as it does in the chlorotic girl. In young men's anaemia,
therefore, the specific gravity of the blood may actually rise above the normal mean (Lloyd Jones). Again, the blood may be defective, or, on the other hand, unduly abundant in salts. These variations are less important, as they are probably integral parts of the former changes: for instance, the salts probably depend directly upon the quantities of the albuminous elements of the blood; the water likewise may rise and fall in part with the albuminous elements with which it is more or less loosely combined: moreover, it is dependent upon the saline density of the blood. Intimately speaking, therefore, while the causes of anæmia may be infinite, the number of anæmic permutations may be few (19). As I have said, however, we have in this chapter to deal with anæmia in its dynamical rather than in its statical aspects; with anæmia which, under favourable conditions, admits of more or less rapid readjustment with recovery of equilibrium.

Anæmias of such kinds may be divided into (a) those in which consumption of the blood is accelerated; (b) those in which renewal of the blood is slow; and (c) those in which both sources of failure are combined. Of the first, fever may be taken as an instance; of the second, inanition from whatever cause; and in pulmonary phthisis, if both appetite and digestion be poor, we shall recognise the mode in which undue rapidity of consumption may conspire with imperfect renewal.

It need not be said at large that such conditions as these merge by insensible gradations into health. For example, in growing youth rapid use of the blood may not be made up even by good appetite and digestion; in old age, although the use of the blood may be slow, appetite and assimilation may be slower still. Again, in direct loss of blood, or in the infection of the blood by some poison, recovery of health is to be anticipated. We shall not forget, however, that waste of blood is far more mischievous and dangerous in old persons; and in those, whether old or young, in whom restoration of the plasma and of cell growth is for some reason imperfect.

Apart from the graver diseases, then, we should expect to find anæmia more frequent and more obstinate in the young on the one hand, and in the old on the other. Some persons are anæmic, or have a bent to anæmia, all their lives long; but simple anæmia is less apt to occur in the decades between thirty and fifty, for at these ages perturbations of nutrition are better resisted. Some persons seem to have a richer blood store than others, to resist the incursions of injurious agents more successfully, and to recover more quickly from such incursions.

Symptoms.—Of the symptoms of anæmia I shall say almost enough under the head of chlorosis, to which these considerations are but introductory; still the symptoms of chlorosis are not merely those of anæmia; and it may be well to ascertain how far the phenomena of chlorosis are peculiar to this state, and how far they are common to anæmia of whatever origin. The main distinction in the phenomena is in the condition of the pulse, which in anæmias of failing quantity is not only quickened but also feeble and empty. In chlorosis, as we shall see, the pulse m
be full and of good or even of excessive pressure. Another side of this peculiarity is seen in the action of the heart, which in anæmias secondary to serious disease may be feeble and almost impalpable, while in chlorosis it is often irritable and sometimes obtrusive. Fatty changes in the heart are common in their degrees to all anæmias. In chlorosis the anæmia tells rather on the respiration and on the steadiness of the heart; in other anæmias, or in many of them, the effect is rather marked by slackness of the cerebral circulation and syncope. Wasting, generally speaking, is not a very prominent symptom in anæmias, and it is rarely seen in uncomplicated chlorosis. The pathology of anæmia will be discussed incidentally under the chlorosis.

The diagnosis, prognosis, and treatment of anæmia depend upon the primary malady of which the anæmia is a symptom—as of syphilis, plumbism, malaria, and so forth. For the most part anæmia is a symptom rather than a disease; even in chlorosis there is no doubt some specific series of antecedents which as yet is hidden from us. On the other hand, as I have already said, in some persons, in whom the hæmopoietic capacity is habitually low, anæmia may be the primary factor; in these cases the proteid elements of the fluid seem to be as much in defect as the hæmoglobin, yet iron is nevertheless an important means of cure or relief. Thus it would appear that iron, the specific action of which in anæmia is hard to explain, does more than feed the red corpuscle; it seems to possess some property of stimulating the growth of the blood as a tissue.

**Chlorosis.**—**Definition.**—Chlorosis is a malady of women, and primarily of young women at or about the age of puberty; it consists in defect of the red corpuscles of the blood, a defect partly of numbers, chiefly of hæmoglobin; the plasma being constant, or even enriched.

Under one name or another chlorosis has attracted attention from early times, yet it was not until the clinical studies of Hoffmann and of Johann Duncan gave accuracy to the description of the malady that it took a definite place in nosology. Ashwell was the first physician to recognise chlorosis as something more than a symptomatic anæmia; and Hayem the first to place the disease on a firm pathological basis.

**Causation.**—It would serve little good purpose to dwell on the fanciful views of the causes and characters of chlorosis which have prevailed among physicians and poets—views which are adumbrated by the use of such names as febris amatoria, icterus amantium, and so forth. We shall see hereafter that the attribution of chlorosis to perverted or thwarted sexual impulses is mistaken, except in so far as an emotional disturbance of whatever origin may contribute to the causation of the malady. On the other hand, although we may have cleared our minds of certain false preconceptions, we cannot yet pretend to be in possession of much more accurate knowledge of the causes of chlorosis. Many and various are the surmises; and of these, or of some of them, I will try to give an account.
CHLOROSIS

Heredity.—That chlorosis is hereditary in no small measure seems to be believed by most observers of the disease, and certainly accords with my own experience. In family after family do I remember the daughters, one after another, as they arrived at puberty, coming for aid in this disorder. It may be replied that as chlorosis is so common a malady it will naturally appear in most or all families as the girls grow up. Still, making all allowance for this confusion and for similarity of conditions, I agree with those who say that chlorosis in its more strongly marked forms tells especially upon certain families; and that in such families the girls are hit more hardly and resist treatment more obstinately than in others. Whether the bent to the disorder may run in a latent channel through the fathers, I cannot say; it seems rather to run through the mothers, as I have found that in families of chlorotic girls the mother commonly says that she and her sisters suffered likewise in a notable degree. I regret to say that I am old enough now to see in my consulting-room the chlorotic daughters of women whom years ago I had treated before their marriage for the same disorder. Dr. Lloyd Jones has published certain opinions on the heredity of chlorosis which I shall more conveniently discuss in the following paragraph:

Sex.—Between the extreme opinions of Dr. Lloyd Jones and those of Dr. Simon, the one holding that chlorosis is wholly and peculiarly a disease of women, and the other that chlorosis is little more than an anaemia of ill-thriven young people, there is a great interval. Dr. Jones, in a series of papers which are remarkable not only for speculative ability, but also for industrious investigation of the phenomena of chlorosis, expresses some such views as the following:—In chlorotic women the specific gravity of the blood falls: on further inquiry it seems that this fall is due to defect in the corpuscular element, and that when the plasma is tested separately the specific gravity is not only up to the normal standard, but may exceed it. In this important respect the blood of chlorosis differs from that found in ordinary anaemia, in which the specific gravity of the blood tends to rise while that of the plasma alone tends to fall. Again, the serum in ordinary anaemia is deficient in quantity, but that in chlorosis is abundant. The first kind of anaemia (oligæmia) may occur in either sex indifferently; the second is peculiar to women in the child-bearing period. In the treatment of this second kind iron is of specific value, in that of the first its value is less certain.

Dr. Jones then goes on to say that the anaemia marked by abundant plasma, and deficient haemoglobin—that of chlorosis—is peculiar to women, and is found in women who come of large families,—in women who have many brothers and sisters. Since these observations were published I have questioned my own experience, and, so far as impressions go, I am disposed to think that the author is right in this respect. Dr. Jones goes one step farther, and asserts that in large families the blood of the sons as well as of the daughters has the chlorotic bent; its plasma is abundant and of good specific gravity. From these facts he infers that this kind of blood is the blood of fertility; and that chlorosis is the
exaggeration of the fertile blood, of blood, that is, which has for its end the storage of nutritive material for the foetus during pregnancy. That such a leaning should be seen in the blood of women at puberty thus becomes comprehensible. These opinions are based on a large number of observations both clinical and pathological, they are coherent and interesting; whether they are true cannot be settled at present. Meanwhile they hold the field, and they make a good working hypothesis, one which has this in its favour, that, to close observers, perhaps every girl passes, as it were, through the outer court of chlorosis in her progress from youth to maturity. One other point seems to me to be in its favour, namely, that the causation of chlorosis is probably simple; the symptoms being uniform, and general in their incidence on one sex, it is probably due to some widely acting antecedents of a kind not subject to much perturbation. Whether Dr. Jones’ hypothesis be true or not, we are probably near the discovery of some such cause of general operation deflected but little by contingent causes. For this reason I think that the conceptions of causes of more multiform or incidental activity, which we shall presently consider, are less likely to be true. Some of Dr. Jones’ results, such as the maintenance of the volume of the plasma, are corroborated by Rubenstein; and the persistence of its specific gravity is verified by Hammerschlag. Dr. C. F. Martin says, on the other hand, that if a relative fall in haemoglobin be taken as a test, chlorosis occurs in men also. He gives four cases, estimated by Fleischl’s method (duly controlled), in which with corpuscles from 4,800,000 to 5,300,000 the haemoglobin fell to 68, 72, 77, 77 respectively; he does not state whether these men were members of large families. My own experience is that the occurrence of chlorosis in men is either unknown or very rare; certainly no observations to the contrary can be accepted unless a careful examination of the blood be recorded.

Race and climate.—We are told that chlorosis obeys no climate, no latitude, no altitude. Hirsch tells us that it is found in Asia Minor, in Algeria, in the West Indies (Creoles), and so forth. I have seen it abundantly in South European races, such as the Italian, and in women of all builds and of all breeding; at the same time, without records of examination of the blood, statements of this kind have but an approximate value. It is said that anaemia is commonest in blondes; and Lloyd Jones adds that blondes are more fertile. I am not satisfied that chlorosis is commoner in blondes; the assertion is open to the criticism that in the blonde it is more conspicuous; indeed the district with which the observer is conversant is no small element in his experience.

Age.—Chlorosis is a malady of puberty; if it occur in later life, as no doubt it often does, the attack may assuredly be regarded as a relapse. All authors agree that a first attack rarely appears after the age of 24. Professor Stockman gives 23 as the highest age of his series. Now in this respect it is remarkable that Leichtenstern found in the age period from 18 to 25 that the haemoglobin is ordinarily about 8 per cent less than in the period from 25 to 45 years of age. Sørensen sub-
stantially corroborates this statement. Stockman (54), in a series of 63 cases, found that no fewer than 41 lay between the ages of 15 and 20. Sørensen attributes this diminution of red corpuscles directly to menstruation; Stockman to the demands of puberty in a more general sense, digestion and appetite being, moreover, often impaired at a time when menstruation is being established.

**Conditions of life.**—Almost every defect in the circumstances of life has been regarded as a direct cause of chlorosis; that such defects continually intensify the disease is admitted by all observers. To work in a badly ventilated room will keep up chlorosis, or anaemia at any rate, in spite of remedies. Some overwrought and underfed women only keep going by taking iron, from time to time, for the best part of a lifetime. Still, an accelerating cause is not necessarily a principal cause. Mental strain, again, is rather a favouring condition than a direct cause. Dyspepsia, with consequent inanition, takes an important place in the causation. In about one-half of Professor Stockman’s cases disorders of digestion were present; so that if the primary cause do not lie in the stomach it is probable that malassimilation is a favouring condition. Dr. Simon lays great stress on the dyspeptic element in chlorosis; he tells us how capricious the appetite becomes in young girls, nay even depraved; such stuff as slate pencil and the like being devoured. There is, indeed, an especial proneness in chlorosis to atonic and perverted gastric functions, if not to actual dilatation of the stomach. Many young women, as their frames develop, fall into a panic fear of obesity, and not only cut down their food, but swallow vinegar and other alleged antidotes to fatness. Nearly all chlorotic girls are disposed to shirk meat and to feed rather on pasty and sweetmeats; and of the meat which is eaten, browned and burnt fragments form no inconsiderable part. If these ingesta do no direct harm, at any rate they conceal a process of inanition; and a fall in nutritious food quickly leads to a fall in red corpuscles. These losses the full-grown woman may recover from readily; the growing and developing girl cannot so easily make up the larger arrears. Yet, after all, as careful observers like Professor Stockman record that only about 50 per cent of chlorotic women are dyspeptic, we cannot regard dyspepsia as a necessary antecedent; the primary cause lies deeper. We have only to look at the peasant girls who come with chlorosis to our rural hospitals, and again at the young maid-servants in good families, to see at once that chlorosis is in its essence independent of food caprices, city life, hard conditions, and indigestion. The healthy country girls may show the malady less; it may fall on them with less average severity the better their conditions of life; at any rate, they may recover more quickly; still chlorosis does not pass them by. Niemeyer testifies to the numbers of robust peasant girls from the surrounding villages who were wont to present themselves before him with chlorosis. Meinert presses this kind of explanation in a special form: he attributes chlorosis to tight lacing or to the belts worn by women; these practices, as he alleges, lead in a considerable percentage
of women to splanchnoptosis; he records gastrophtosis in most of his patients who suffered from the malady, and in 15 per cent he reported movable kidney. Surely, of movable kidney, at any rate, this is an exaggerated proportion, and one opposed to the reckonings of all physicians who have studied these dislocations (vol. iv. p. 342). As regards the stomach, I feel impelled to surmise that in many cases Meinert must have taken toneless and inflated stomachs for dislocated stomachs; no reports on this subject are worth much unless the line of the smaller curvature be plotted out.

Estimates of the hydrochloric acid present in the stomach in cases of chlorosis have been made by many investigators. In some this acid was found in excess, in some in defect; in others, again, it proved to be normal in amount. Similar results would probably be obtained in any group of sickly young persons.

It is a common experience that many girls otherwise healthy and living under the best conditions of life become chlorotic: perhaps no girl escapes it altogether; some, however, show it but little, and recover rapidly. The secret does not lie in inanition or dyspepsia.

A more potent cause, perhaps, is emotion; either emotion of a wearing and long-continued kind—such as love sickness, home sickness, and the like, or shocks of a more sudden onset. A remarkable case of this kind came under my notice a few years ago. A young lady became very chlorotic, and her cure was not so easy as usual; however, after a little patience she was apparently cured, and the treatment was continued until fear of relapse had abated. On a certain evening, soon afterwards, the other members of her family having gone out till a late hour, she went to bed alone. At midnight she was awakened by a sense of some presence in the room, and on opening her eyes she saw a figure in white moving across it. She lay speechless with terror until the apparition, after some pacings, passed out of the room again. As it issued from the room she became aware that the ghost was the butler in his night-shirt; and she sprang out of bed to bolt the door after him. As she did so he returned towards the door, and, thrusting against it, tried to re-enter the room. With strength renewed by fear she thrust against him, and after some effort she secured the door. The man hung about the landing for some time, and she sat on her bed in an agony of apprehension until her parents' return home, about four o'clock in the morning. It turned out afterwards that the poor man was a sleep-walker, and his promenades innocent enough. On the next day, however, the chlorosis was profound, and she was brought to see me again in a worse plight than before. I was assured by the girl's mother that when they left the patient on the evening of the alarm she was to all appearance well; by daylight next morning she was seen to be as I saw her. Other cases of the same kind are on record. Still, such a mode of causation is uncommon, and probably depends upon a strong proclivity to the disease.

Generative organs.—The fashion of attributing chlorosis to sexual disturbances of which the patient may or may not be conscious is passing
away. The final extinction of this hypothesis we owe to Rokitansky and Virchow, who proved by necropsies that no constant morbid condition of the organs of generation is found in these cases: the parts may be normal; or this or that abnormality, such as hypoplasia, may be discovered: but all or any are of an incidental kind, and present no common factor. At the same time, if epithelial débris be found repeatedly in the urine, masturbation must not be forgotten, and corroborative evidence of the habit may be detected.

Mesoblastic hypoplasia.—Morgagni, Meckel, Rokitansky, and, still more definitely, Virchow have drawn attention to a peculiar arrest of development of the arterial system found after death in certain cases of chlorosis. [Vide art. "Diseases of Arteries."] Such necropsies are few, for it is only by accident that cases of chlorosis come to the post-mortem table. In the cases before us a very strange state of things is revealed. The aorta may scarcely admit the little finger, and the abdominal portion of the vessel may be no bigger than the ordinary iliac or femoral artery. This remarkable arrest of development is seen to be but a part of a general arrest throughout the whole arterial system, and is supposed to indicate a like hypoplasia of the mesoblastic layer throughout, including the blood-forming organs; hence, it is said, the peculiar anæmia. This explanation is rather of the dead-house than of the bedside. That a disorder so common and for the most part so curable should depend upon a malformation so grave and so incurable as this aortic and general vascular hypoplasia is on the face of it highly improbable. Again, so far as our evidence goes, the arrest may occur in either sex indifferently (Hayem). It is said, indeed, that Virchow was not always careful to exclude the cases of congenital or slow heart disease with which a hypoplasia of this kind may be bound up (Pye Smith). Be this as it may, Virchow's doctrine has a great vogue in Germany; and it would ill become us to deal lightly with a well-considered opinion expressed by a pathologist so eminent.

Hæmorrhage.—Loss of blood is a common and direct cause of anæmia, and has been assumed to be the primary cause of chlorosis. It is said that in many cases hæmorrhage is or has been obvious enough; whether in the form of menorrhagia, epistaxis, hæmorrhoids, hæmatomesis, or otherwise. And it is urged, if hæmorrhage be a vera causa, and in a considerable number of cases an immediate factor, may not hæmorrhage be the general cause; hæmorrhage which, if it issue by some passage unobserved, or in repeated quantities too minute to catch the eye, may often be overlooked? Such imperceptible oozeings have been supposed to occur into the stomach, for example.

Now we have seen that the anæmia which results directly from hæmorrhage is not quite identical with that of chlorosis; that it is revealed rather by a diminution in the number of the red corpuscles than by their defect in hæmoglobin; this proposition, however, is far from established. Yet there can be no doubt that chlorosis occurs daily in which, after the closest inquiry, no hæmorrhage can be seen or heard of: and in respect of the alleged persistent oozing of blood from
mucous surfaces the contents of the stomach have been repeatedly tested without the discovery of any reactions due to blood or sanguineous effusion. That menstruation or other blood loss, even if moderate, may aggravate chlorosis is certain, and amenorrhoea, therefore, is often a protective condition; but on the other hand chlorosis, as we all know, may occur in girls before the appearance of menstruation. The effects of haemorrhage on the specific gravity of the blood plasms have yet to be determined.

Bunge's hypothesis.—A very ingenious hypothesis in explanation of chlorosis, and of the behaviour of iron in the cure of it, has been proposed by Bunge. I will set forth the hypothesis in the lucid words of Professor Stockman:—

“Bunge holds that the ordinary preparations of iron, including the so-called albuminates and peptonates, cannot be absorbed from the alimentary canal. He points out that ordinarily the iron of the red corpuscles is formed from the organically combined iron in the food, which is something like haemoglobin in constitution, and can be readily absorbed and readily converted into hemoglobin. From milk and yolk he isolated such an organic combination. But he admits that inorganic iron preparations are capable of curing chlorosis, and explains this as follows. In chlorosis digestion is disturbed with formation of sulphur-{}-etted hydrogen and alkaline sulphides in the bowel. These combine with and separate out the organic iron of the food, and sulphide is formed, an inorganic compound which, according to Bunge, cannot be absorbed; hence the blood loses its necessary supply of iron, and chlorosis results. When inorganic iron is given, however, it combines with and neutralises the sulphur-{}-etted hydrogen, and thus protects the organic iron of the food, which, therefore, becomes absorbed, and goes to form haemoglobin. In support of this view he adduces the received opinion that large doses of iron are necessary for the cure of chlorosis, and this he says is because large amounts are necessary to neutralise all the sulphurated hydrogen in the bowel. Further, he states on the authority of Zander that hydrochloric acid cures anaemia more satisfactorily than iron does, because it is antiseptic, and prevents formation of sulphurated hydrogen in the bowel.”

Now, as Stockman adds, “the presence of iron in our food, in the tissues and excretions of the body, its constant ingestion and excretion, and the small quantities with which we have to deal, apparently place a complete barrier in the way of rigidly proving by chemical methods that it is or is not absorbed.”

Stockman met these difficulties by other expedients. First, in certain well-marked cases he removed the problem from the sphere of the bowel, and endeavoured to bring about the cure of chlorosis by injecting iron subcutaneously. Secondly, he administered sulphide of iron by the mouth, a preparation which cannot take up more sulphur, and, being non-astringent, cannot be credited with any tonic effect on the bowel such as might promote its absorptive activities. Thirdly, he administered bismuth, manganese, and other drugs which have a like power of neutralis-
CHLOROSIS

...ing sulphuretted hydrogen, and which should therefore have a like curative power in chlorosis. The results of these observations were as follows: both in his own cases, and in the cases of others who had given iron subcutaneously for other reasons, iron thus administered subcutaneously cured chlorosis, though the method is one which has its drawbacks; Dr. Warfvinge of Stockholm cured a series of cases by subcutaneous injection of iron, and found that thus used one-fifth of the ordinary doses of the metal sufficed: the cure of chlorosis seems then to be by absorption. Secondly, sulphide of iron proved a satisfactory means of cure. Stockman also emphasises, what many of us had noted, that reduced iron cures chlorosis in doses too small to have any substantial effect in neutralising sulphuretted hydrogen. I may add that patients have complained to me that reduced iron seems, indeed, to have the unpleasant property of disengaging sulphuretted hydrogen in the bowel, so that the drug is sometimes quaintly shirked by the patient. Thirdly, Stockman found that bismuth, which would absorb even more sulphuretted hydrogen than iron, is nevertheless quite inefficacious in the treatment of chlorosis. Kletzinsky speaks, therefore, in paradox when he says that “from all the hundredweights of iron given to anæmics during centuries not a single blood-corpuscle has been formed.” Stockman thinks that iron is absorbed as other salts are, the ferric salts being reduced to ferrous in the intestine; and that the building of it into organic combinations, which are of various degrees of intimacy, is done in the liver. Dr. Mackay stated at the Toronto Congress in 1897 that iron is absorbed by the epithelial cells of the villi, the iron of haemoglobin being taken up as haematin. He adds that the metal is passed inwards by the leucocytes. Binz has stated, I think, that an early effect of iron in chlorosis is a multiplication of leucocytes. That they are increased in total number rather than drawn from their hiding-places would be difficult to prove; at any rate they may be more busily employed. That “inorganic iron” given as a remedy does no more than stimulate the atonic intestine to absorb the iron (Kobert) seems improbable. Bunge’s ingenious suggestion seems, then, to be without foundation.

Toxic causes.—That chlorosis is due to the influence of some toxin in the system is a speculation which must have presented itself to many minds; and not a few pathologists have busied themselves with hypotheses of this kind, from the inevitable microbe to the mere absorption of faecal juices from the constipated bowel, or the presence of uric acid in the blood (Haig). Bunge’s hypothesis, indeed, rests upon some such postulates in respect of toxic agents, though in his view the toxins in the bowel act indirectly and within the canal. The toxic hypotheses of chlorosis depend for their proof on the discovery of such injurious agents in the blood or excretions. The simplest of them is that popularised by the late Sir Andrew Clark, who earnestly argued that the impoverishment of the blood in this malady is directly due to constipation of the bowels; this, he said, brings about an accumulation of the products of decomposition in the
alimentary canal which, passing thence into the blood, poison it either in its prime or at its sources. Stockman, Simon, and other observers who have tabulated cases with this problem in view, point out that, in the first place, only about half of the cases of chlorosis present constipation; while, on the other hand, constipated people who do not suffer from chlorosis are common in both sexes. When Clark published his paper I paid close attention to this point, and accepted no mere routine reply to my inquiries into the state of the intestinal functions; and I likewise found reason to believe that, when the cases are excluded in which constipation is attributable to the iron administered, chlorotic women are not more constipated than other women. We shall see presently that this hypothesis of toxicity is not without considerable importance in the field of therapeutics; no one has even pretended to show that chlorosis is to be cured by purgatives alone, yet, on the other hand, I detect in almost all writers on chlorosis a temptation to rely on the toxicity of the blood in one direction or another. Even Lloyd Jones, believing as he does that chlorosis is but an abnormal intensity of a normal storage process, fortifies himself with an argument out of the same quiver; he has tested the ovarian system for such a poison, so far without success, and still has his eye on the uterus as an alternative source. Van Noorden (36) and Arcangeli are likewise disposed to assume some perversion, absence, or excess of an ovarian internal secretion as a factor in chlorosis. Chvostek reported that in twenty-one cases out of fifty-six he found the spleen enlarged; thirteen times it was palpable: thus he also is led to support the alleged kinship between chlorosis and splenic anaemia. Clement, if I understand him aright, looks for the toxin or infective agent outside the body: and, partly on analogy, considers that chlorosis should be classed with the infectious diseases. He tells the story of an epidemic which occurred in a small village, during which eight young girls were attacked with febrile symptoms and enlargement of the spleen; phlegmasia alba, dry pericarditis, and pleurisy were among the complications. Anaemic these patients were no doubt, but few readers will be convinced that the malady under which they suffered was chlorosis. Against these allegations of enlarged spleen I may say that Simon and Schrott, both of whom had their attention directed to this point, found this enlargement in one case each [vide “Spleen in Anæmia,” vol. iv. p. 522; and art. “Splenic Anæmia,” p. 539 of this volume].

Pick finds the source of the blood-poison in another place, namely, in a dilated stomach. His cure for chlorosis is lavage. Nothnagel takes substantially the same view of the matter as did Clark. Now, no doubt, certain poisons do reduce the blood; such poisons as lead, arsenic, syphilis, those of acute rheumatism, Bright’s disease, and pernicious anaemia, and so forth; but it is a superficial way of looking at things to say that anaemia here and anaemia there must be due to like causes. If we are to listen to comparisons of this sort we must have the specific gravity of the blood-serum in all cases, and from it we must learn whether these anemias are all of the same kind; that is, whether the blood plasma keeps up to the standard of health, or even rises above it.
while that of the whole blood falls. Jones tells that such is the feature of chlorosis; and Hayom, Stockman, indeed all careful students, tell us that in experiments and observations on this subject regard must be had to the kinds of the changes in the blood. Chlorosis, as Immermann well says, "maintains its individuality in the teeth of all the attempts that have been made to merge it in the great ocean of anemia."

Again, in anæmia there is, or often is, no evidence of poison in other parts or excretions of the body. For example, Simon (50) says that indican is not found in the urine of the chlorotic; and Rethers, by a series of important investigations, seems to have shaken the foundations of the toxic hypothesis, by showing that in 9 out of 18 cases of ordinary and severe chlorosis the ethereal sulphates were absent; and that in the remainder there was no uniform or considerable appearance of them. Von Noorden, who (p. 347) discusses this point clearly, quotes Hennige and Heinemann to the same effect; and Stockman adds the testimony of Mörner. The secret of the causation of chlorosis does not seem to lie, then, in a foul state of the intestine, or in the absorption of some poison; the evidence lies in the direction of diminished manufacture and metabolism rather than of accelerated destruction. The very poorness of the urine in many cases of definite chlorosis, its actual deficiency in colouring matter, indicates that, instead of an excessive breaking-down of blood corpuscles, such as results from the absorption of poisons of the kind under consideration, the life of the red cells is, on the other hand, prolonged.

There seems to be a certain, though probably not a very intimate, association between chlorosis and Graves' disease. Chvostek gives seven cases of chlorosis associated with Graves' disease. Lloyd Jones and others also note some fulness of the thyroid in many cases. I have observed the same coincidence; but without a calculation of the frequency of some fulness of the thyroid in healthy women it is not easy to express an opinion on the point. Professor Stockman supposes that chlorosis depends mainly upon two causes; namely, on insufficient food at the age of development, in which conclusion he is supported by Simon, and on the persistent effects of incidental hæmorrhages, menstrual and other, which may be positively excessive, or relatively excessive in the individual case. When, however, we regard the many contingencies to which the operation of these several causes are open, the partiality of their incidence, and the many cases in which these factors produce disorders other than chlorosis—such as mere emaciation and debility, with a fall in the proteid value of the blood—I repeat that, in my opinion, we have to look for a more uniform cause, one more independent of contingencies; such, perhaps, as that proposed, rightly or wrongly, by Dr. Lloyd Jones.

I fear Dr. Haig's uric acid hypothesis has little to support it; against it we find on all hands that the excretion of nitrogen in chlorosis is rather diminished than increased. Gräber, moreover, found the alkalinity of the blood up to the normal standard, and even above it; and Von Noorden tells us that Peiper, Kraus, Rumpf, and Dronin corroborate this statement.
Pathology.—In the discussion of the causation of chlorosis we have dealt incidentally with matters of pathology or pathogenesis; the remaining part of the subject will not detain us long. On prick ing the finger of a chlorotic patient, bloodless as she may appear, the blood springs forth freely, more freely than in anaemias of other kinds; the colour also is different; the red corpuscles being fewer, the blood transmits light more readily and the colour is brighter; it is bright red or even borders on orange. The specific gravity of the blood is easily tested by Roy's method, but that of the plasma less readily; for this a centrifugal machine is required. The specific gravity of the blood is reduced; that of the plasma is steady, or possibly even raised. Dr. Lloyd Jones tells us that the mean specific gravity of the blood rises in both sexes alike till puberty; at this period, however, that of the man still rises, while that of the woman falls. Taking the blood of childhood (two to three years) at 1050, that of a young man of seventeen may be 1058; of a young woman 1055-6. These observations have been made, of course, under dietetic and other controls. From the age of seventeen, then, Jones finds that the mean specific gravity in man still rises; in woman it remains low till twenty-five, after which age it rises to 1055 or 1056. Coincidently with these changes in the blood general metabolism is lessened, for the excretion of carbonic acid and of urea also falls (Landois and Stirling). In the Charts herewith, which I am enabled by the kindness of Dr. Lloyd Jones to publish, these changes are well exhibited. Whether the haemoglobin be increased, unaffected, or decreased during or by menstruation seems as yet undetermined. I may repeat that Dr. Jones says, speaking generally, that the specific gravity of the blood stands at a lower mean in women who have many brothers and sisters; that indeed the specific gravity may be taken, approximately, as a gauge of fertility, the change in the blood in chlorosis being an extreme fluctuation of a physiological quality of the child-bearing period of life. Every girl, then, may be regarded as potentially chlorotic, and perhaps none passes through young womanhood without some phase of the disorder. The boundary between the physiological and the pathological states, if Lloyd Jones' conclusions are to be accepted, is an arbitrary one.

The specific gravity of the serum differs little, if at all, from that of health; if anything, it tends to rise. That of the blood falls as a whole by the diminution of the volume of the red corpuscles or of their haemoglobin, usually of both; changes which are commonly recognised in chlorosis. In twenty-six cases tabulated by Jones (p. 22) the fall of the number of red corpuscles comes out strongly, so strongly as to teach us that this fall, taken together with a like fall in haemoglobin value, is more characteristic of chlorosis than we are wont to suppose; at the same time the proteid value of the blood keeps steady. The alkalinity of the blood, especially of the plasma, as here said, is usually increased.

The reader thus perceives that the features recognised in chlorosis are the converse of those seen in some other forms of anaemia, such, for example, as ankylostoma and pernicious anaemia.
Chart 2.—Showing the results of observations on the specific gravity of the blood of healthy males of different ages, and the upper and lower limits of variations consistent with health (Lloyd Jones)
Chart 3.—Showing the results of observations on the specific gravity of the blood of healthy females of different ages, and the upper and lower limits of variation consistent with health. (Lloyd Jones.) The two charts represent observations on 1400 individuals.
Chart 4.—Showing the variations in the specific gravity of the blood in healthy women, from 2 to 42 years of age, and the results of observations upon 120 young women with chlorosis. (Lloyd Jones.)
In Professor Stockman's no less careful inquiries the bearing of diet on chlorosis is estimated. That the iron needed for the blood is absorbed from the food seems probable, nay, it is proved. It is certain that the chick gets iron from the yolk, and the suckling from the milk. Stockman has estimated our sources of this metal. He takes the issue of iron daily as $\frac{1}{10}$ of a grain, and he found that the daily food of fifteen healthy persons contained iron at the rate of $\frac{1}{10}$ to $\frac{1}{3}$ of a grain; thus the supply is equal to the demand: moreover, detained in the liver, there is a store of disengaged iron, the precipitate of defunct corpuscles, which acts as a reserve; in healthy livers Stockman found from $2\frac{7}{10}$ to $4\frac{3}{4}$ grains of it. Now if we compare this estimate with the state of chlorosis we find a derangement of these relations. Although in women, owing to menstruation and so forth, the reserve iron in the liver is less than in men, yet their food is apt to contain a smaller supply of the metal. In the habitual diets of four chlorotic women Stockman found iron in the respective quantities of $\frac{1}{10}$ to $\frac{1}{3}$ of a grain a day; so that if iron be escaping at a rate of $\frac{1}{10}$ of a grain daily, the red corpuscles may well starve. Coppola and other observers fed animals (cocks and dogs) on food from which all iron had previously been removed; the haemoglobin value of the corpuscles soon fell, but was readily replaced on the administration of inorganic iron. It was found that on a non-ferruginous diet the haemoglobin fell 35 per cent. It is to be remembered that the iron is held in various degrees of intimacy in the articles of diet; in some organic molecules, as, for example, in the protoplasm of cells and nuclei, the combination may be so intimate that ordinary tests fail to detect it; and the metal has to be recovered by incineration (Zaleski, Vay). In ordinary anaemia of an accidental kind—as, for instance, after an occasional haemorrhage—the food iron commonly proves to be sufficient for the restoration of health; although, if 20 grains of iron be lost, the food may be long in making it up. I have said that the defect of the blood in chlorosis usually extends to the number of corpuscles as well as to the haemoglobin contents. Both Stockman and Lloyd Jones insist on this defect; Stockman, in his cases, reports a "striking deficiency of red corpuscles as well as of haemoglobin." A deficiency down to two millions may be observed, but it rarely falls lower. Stockman's highest figure was 66 per cent, his lowest 20 per cent. In four days after beginning ferruginous remedies the corpuscles go up with a bound, and in 10 or 14 days reach the normal standard; the haemoglobin rises much more slowly, and two months after the beginning of treatment may still be defective. Deformity of the red corpuscles is not a feature of chlorosis as it is of pernicious anaemia; but a considerable proportion of them may be under-sized, even when full allowance is made for the presence of microcytes, and their vitality is said to be low; that is, their histo-chemical properties fall, and they fade before doing full work. The relations of water and of salts to the serum of the blood are less easy to discuss: the steady specific gravity of the proteids in the plasma would indicate that there is no tendency to hydramia. It seems probable that the amount of water
stands in some definite relation to the proteid constituents, as its presence is not a mere dilution, but a combination with these substances: in like manner the salts are related to the state of the proteids and to the cell activities. For the present, however, it does not seem that these are points of primary importance in chlorosis.

Coagulation is slower in chlorotic blood, outside the body, notwithstanding the tendency to thrombosis within it; the clots are scanty, and the fibrinogen is less, facts which are not easy to reconcile with such an accident. A slow venous blood-stream may account for the tendency to thrombosis.

We can only guess at the mass of the blood in any case; in many anæmias we have seen that the mass of the blood seems to be diminished, the blood issues slowly from a puncture; in chlorosis the fulness of the vessels seems to point to a persistence of the normal blood mass, and such is the assumption of most writers. Dr. Lloyd Jones thinks that the dyspepsia of chlorosis is due to an accumulation of blood in the great veins of the abdomen, the dilatation of which he attributes to some influence on the splanchnic nerves. If there be an increase in the mass of the blood, there may be an actual "plethora serosa," with or without hyperalbuminosis. If the aorta be small, there may be a relative plethora. In some cases of prolonged chlorosis there may possibly be some mesoblastic hypoplasia of a transient kind, and the capacity of the arterial tree may grow with its nutrition and its contents. In ordinary cases, however, the plasmatic elements of the blood seem to be sufficient for vegetative growth; chlorotic girls do not lack size, nor do they fall away from the main lines of development.

On the other hand, the heart and vessels are subject to deterioration of a somewhat serious kind. The arteries, and especially the aorta, near the origin of its ascending portion, may present on the inner coat dull yellow spots and strie; indeed, superficial erosions of some extent may be detected. The strie may also be seen in the descending portion on its posterior inner aspect, between the intercostal and lumbar arteries (Virchow). These patches and streaks, when examined microscopically, are found to consist of minute dots, each, according to Virchow, being a fatty connective tissue corpuscle. The heart is commonly of normal size, but it may be moderately dilated. Valvular disease is rare, as is ordinary atheroma; but fatty degeneration of the heart is a feature of chlorosis, as of all anæmias. The change is primary, and is best seen in the papillary muscles, especially of the left ventricle, as spots and strie; healthy fibrils being mixed with fatty. Virchow also describes fatty degeneration in the capillaries.

The renal, hepatic, and gastric cells are fatty also, and all the organs are pale. The atonic stomach may be dilated. The spleen, marrow, and lymphatic glands are not understood to be abnormal.

Symptoms.—The chlorotic girl is known in every consulting-room, public or private. The disease is no respecter of rank or of fortune. Whether her aspect at first sight be indicative of the disease or not, her characteristic complaint is dyspnea. Dyspnea, due probably to incessant stimulation of the bulb by suboxidised blood, is more persistent and incapacitating in chlorosis than in any other disorder, except, of course, in

VOL. V  2 K
advanced organic disease of the heart. Many of these patients bear in their features the classical sign of their malady, but not so all of them; many of them carry some colour (chlorosis florida); but in my experience all suffer from dyspnea, and, however insidiously it creep on—for the disease may attack acutely or insidiously—the patient is never unaware of it. If she be asked whether she can trip upstairs as she was wont to do a few months previously, her answer will bring the physician near to his diagnosis. I have said that many chlorotic girls carry some colour, indeed a high colour. In past years this was a little puzzling to me, as no doubt to others also; but we have now learned to look below the surface, and I see that Stockman, Lloyd Jones, and many others deal with this aberrancy, and point out why even a high colour may not be incompatible with chlorosis. It is said that the conspicuous chlorotic is a blonde; but surely we see many blondes who in spite of an assured chlorosis have some carmine in their cheeks, and many brunettes who are pale enough and green enough to reveal their disorder. Much depends, I suspect, upon the skin of the individual; a fair and clear skin takes the alabaster or old wax colour, a brown and a muddy or thick skin does not. We have blondes with bad complexions and brunettes with transparent complexions. Transparent skins are often seen in the dark women of the so-called Iberians among ourselves, and chlorosis is manifest enough in them; on the other hand, I know many blondes who have not presented the standard tint of chlorosis, although suffering from it in no slight measure: in such persons a thick complexion conceals or modifies the characteristic tints; grayness or sallowness takes the place of marble or alabaster, and chloasmic tints may be seen here and there on the temples and about the knuckles and other joints. Such women do not flush readily or deeply, and their limbs, often rough and hairy, do not offer a good surface for the display of the changes of the blood. The upper part of the chest, bared for the stethoscope, may, however, manifest the peculiar hue; a pallor may be detected also in the lachrymal caruncle, on the under side of the conjunctiva and the mucous membrane of the mouth; the sclerotics may be blue, the pupils dilated, and the ear—that useful signal of variations in the colour of the blood—may be white. The nails, also, and the blue veins on the skin may have their story to tell.¹ The pupils

¹ For the following ingenious method of measuring the oxidising activity of the blood in chlorosis I can say nothing of my own experience: I therefore put it into a note. The passage is translated and a little abbreviated from Henocque, "L'hémostoscope," Gaz. hebdo. Oct. 23, 1886, and April 1, 1887. It is quoted by Gilbert (10).

The reduction of oxyhemoglobin into hemoglobin in the tissues can be determined by spectroscopic examination of the blood through the thumb-nail. Thus the first band characteristic of oxyhemoglobin may be seen, sometimes the second also. If a ligature be tied round the phalanx the bands disappear, the yellow on the level of the line D reappears, which was concealed, and then the bands vanish. The ligature isolates in the thumb a certain quantity of oxygenated blood, which for a certain time exhibits the bands of oxyhemoglobin; the latter gives off its oxygen to the tissues, is reduced, and the absorption band is no longer intense enough to traverse the nail. In the normal state this process occupies 70 seconds, and the quantity of oxyhemoglobin thus reduced is 0.20 per second. This is taken as the unit of reduction. In chlorosis the oxidising activity falls to 0.05–0.19 of this unit, the mean fall being 0.44.
CHLOROSIS

are often dilated, brightening the eye, though the face is often described as
inanimate and puffy; perhaps this word "puffy" is not a very accurate
one. If chlorosis be a disease in which the proteids of the blood are not
wanting, and if the mass of the blood be not diminished, the face may
retain its ordinary contours and yet seem, as it were, puffed by contrast
with other signs suggestive of serious ill health. In this kind of chlorosis
epistaxis may occur, even profusely. It is preceded by a sense of fulness
and discomfort, and is followed by a sense of relief. In the anemias of
malaria, plumbism, or cancer, the vessels are more empty and the face
more shrunken. Chlorotic girls still blush readily enough, and even in the
height of an attack of their malady some of them never lose a vivid carmine
on the malar eminences. There is another peculiar sign to be seen in the
face: Dr. Lloyd Jones says that if a healthy person be asked suddenly to
look up at the ceiling, without moving the head, the eyebrows are raised
and the forehead is thrown into horizontal folds by a contraction of the
anterior portion of the occipito-frontal muscle. Now, in many chlorotic
women this associated movement of the occipito-frontal muscle is wanting;
as Joffroy pointed out also in Graves' disease: yet they can contract this
muscle if they try to do so. Lloyd Jones attributes this lagging to a
lessened irritability of the skeletal muscles, due to lack of haemoglobin;
and thus it is that the face appears inanimate or even apathetic, the
languid, listless look of chlorotic patients being partly due to want of
facial expression, partly to slackness of the limbs (Hayem). Sydenham
says that "erurum tensiva lassitudo" is a complaint of these patients.
Yawning betrays a like muscular affection, and to the patient is often a
troublesome symptom.

Digestive system.—The tongue is pale, moist, indented, and often clean.
At other times it presents on its coated surface some evidence of disorder
of the stomach or associated organs. The breath likewise in some
patients is heavy in odour. Such patients are often constipated, though
great constipation is consistent with a clean tongue. That constipation,
however frequently seen, is not by any means a constant symptom I have
already pointed out. It seems to be noted in about one-half of tabulated
cases.

The stomach is often the seat of some morbid changes; it may
be permanently dilated, though more often temporary distension and
atony may simulate such dilatation. I am not prepared to say that
dilatation in the formal sense of the name is so common in chlorosis as to
make a part of our ordinary conception of the malady (vol. iii. p. 494);
or do I regard it as a very common complication: were it so, the cure
of chlorosis would be a matter of more serious difficulty than it is.
Dyspepsia of the subacute or chronic catarrhal kind, or that of flatulence
and atony, sometimes stops the way, but it rarely defies the usual means
of treatment. The appetite may give us more trouble. I have said
that it is often marked by caprices and perversions which put serious
obstacles in the way of nutrition. At the same time these symptoms
are seen in other states, such as neurasthenia—the dislike of meat
especially—and are, perhaps, characteristic rather of the kind of patient than of the kind of disease. In neurasthenia this anorexia or parorexia leads to emaciation; in chlorosis this is not generally the case. In anorexia nervosa (Gull) the wasting is also remarkable; but the chlorotic woman eats more: her blood is also richer in proteids, and being short of oxygen permits the deposit of fat. The relations of chlorosis to ulcer of the stomach are dealt with in the article on the latter subject (vol. iii. p. 519).

Diarrhoea is a rare and incidental occurrence. Hysterical chlorosis is more compacted of fantasy, bizarrerie, and caprice than the common and uncomplicated form of the disease; or tears and melancholy may alternate with fretfulness and self-importance. "Hysterical or barking cough" is a very trying feature of these cases; indeed, I have found it a not infrequent feature of chlorosis not otherwise marked by hysteria or neurosis. Such coughs may be interpreted by an examination of the blood, and cured by iron; for indeed they are rather chlorotic than hysterical in nature.

Circulatory system.—Sydenham describes "pulsus febrilis" as a symptom of chlorosis; and later authors, relying on the thermometer, describe a "febrile chlorosis." Were not such observers as Prof. Osler in their ranks I should be content to say that "febrile chlorosis" is an aberrant form of the malady, and the fever may prove to be significant of some complication. The use of such a name by less experienced physicians might, for instance, lead to confusion between chlorosis and pernicious or syphilitic anaemia, or some other anaemia due to a toxic agent. I should be content to say that the temperature in chlorosis is not subnormal, as in anorexia nervosa, for instance; and that it may be apt to rise in trifling measure under the influence of occasional causes. The pulse, however, as Sydenham said, is generally quickened more or less, and is very impressionable by change of posture and the like. In opposition to some authors, I am scarcely disposed to admit that in chlorosis the arterial blood-pressure generally ranges above the normal standard; though no doubt it is characteristic of chlorotic anaemia that such a rise may be observed occasionally; and as a rule the mass of the blood is not diminished, the artery is well filled. Immernann seems to have given vogue to the opinion that in chlorosis the heart increases and arterial blood-pressure rises. Bihler, on the other hand, who has gone over this ground carefully, concludes that so far from the blood-pressure being raised it is usually under the normal mean. Estimations of blood-pressure made with the ordinary sphygmographs are of little or no value. As, generally speaking, the mass of the blood is not diminished, the output of the left ventricle is at least normal in amount, and the arteries are well filled. but this does not necessarily or even probably mean increased blood-pressure. Extension of cardiac dulness is generally towards the right, not towards the left side. As vascular tone increases, the heart returns

1 Dr. Stockman tells me later that he finds that all bloodless people are liable to slight febrile attacks. The cause of this instability is discussed by Gruber and others.
to its normal limits. Chlorotic women are liable to syncopic attacks which seem to indicate that the blood-pressure, if fairly sustained as a mean, is nevertheless subject to great or extreme variations. The arteries often throb in chlorosis; although often these vessels are really full, they are much slackened in tone: we may commonly see pulsation in the epigastrium and in the episternal notch, and both first and second sounds are very loud in the carotids. The second sound is often louder at the apex than at the aortic cartilage.

The heart is irritable; it often palpitates, it may be to the great distress of the patient. The palpitation makes itself felt rather on exertion—on the least exertion; a perturbation due to the call of the anemic tissues, probably the muscles, for more blood, that is for more oxygen; their supply of proteids is probably sufficient. The heart itself, on examination, is found to vary a good deal. Although its beat is often throbbing or laboured, yet not less often it is feeble and ill-defined. That the heart is dilated is the assertion of many observers; however, the facility with which modern physicians delineate and record the varying dimensions of this organ excites my admiration of a skill I cannot hope to attain; the conditions of physical diagnosis seem to me indeed to be too inconstant for such appraisements. For instance, in this and other ailments of young women I have observed (cf. vol. iii. p. 505), and the observation is by no means confined to myself (34), that the mean volume of the lungs is often reduced. The respiration in chlorosis is obviously shallow; and, although to tight lacing is attributed every mischief which may befall a woman, yet it is indeed probable that the fashion of feminine garments prevents the full excursion of the diaphragm; thus in chlorosis the lungs may shrink, and the heart more or less denuded may offer a larger front to the auscultator. In cases of alleged cure of dilatation of the heart we may have a contrary phase; the lungs may expand under this measure or that, and the heart be enveloped over a larger part of its surface than before: in view of such changes as these it seems very difficult confidently to infer, in the one case or the other, that the organ is much altered in size and shape. That in anemia, generally speaking, dilatation of the heart as of the stomach is prone to occur from loss of tone I have already said, but that in chlorosis the heart undergoes an enlargement both in substance and in capacity is not proven. We know, indeed, from the appearance of apex murmurs and the tendency to fatty degeneration, that the organ may yield a good deal; yet a case of chlorosis must be of extraordinary severity to bring the patient to the post-mortem table. Over-exertion under such cardiac conditions may cause "irritable heart" or "weak heart"—symptoms, by the way, which the ailing patient may never get rid of.

Venous murmurs. — The murmurs heard in the heart and veins in chlorosis have been studied with an interest enhanced by the obscurity of their causation. The phenomena are very common, they are demonstrated to every student in the out-patient room, and the problem of their generation is a fascinating puzzle for every ingenious clinician. And
whose cannot himself explain can select his explanation from the teacher whose doctrine he prefers.

The venous hums, which, although they may occur in any anaemia, are very characteristic of chlorosis, may be considered first. These murmurs—known as bruit de diakle by the French, as Nennengerausch or Venensansen by the Germans—the two former names being taken from the humming-top—are most often heard in the jugular veins, usually more loudly on the right side. The sound in the jugular vein is a persistent hum, likened by Sansom to the shell sound which Landor has made his own; Sir Thomas Watson likens it to the hum of a gnat or to that of the wind sighing through a crevice (47). When this hum is loud it can be felt; if the left hand be laid on the neck, grasping it lightly so as to let the thumb rest upon the right jugular, a vibration in the walls of the vein is perceptible to the touch; and by such pressure on the vein as shall stop the venous current the hum is made to cease. It is heard best in the standing position, being favoured by gravitation; and during inspiration. It is clear, then, that the hum is generated in the vein. If the patient be directed to take a deep breath, or to rise from a recumbent to an upright position, the venous current is accelerated and the hum is intensified. The sound is usually louder in the right jugular, because this vessel, by way of the innominate vein, enters the vena cava almost in a right line; whereas the left cervical veins collect and fall into this channel at a considerable angle. Under these and other circumstances the pitch and intensity of the murmur may vary. For the same reason it is sometimes louder during the cardiac diastole; and if, instead of suppressing the sound by stopping the vein, the stethoscope be very lightly pressed on the vessel the murmur may be increased. To turn the head to the opposite side may have a like effect; but the sound is a capricious one, and that disposition which on one day or in one person seems to intensify it, on another day or in another person may extinguish it; often indeed it varies extremely while under continuous observation. It is not difficult to suggest an explanation of the hum; that which is generally given, and which on the face of it seems most probable, is that the vibration of the walls of the vein is due to a change in the calibre of the tube at the root of the neck. The lower portion of the vein is of constant or almost constant calibre; this constancy being secured by the adhesion of the coats to the cervical fascia. Now if by any means, such as a smaller stream of blood, the vessel be narrowed above, there is a run of the blood from a narrower to a wider channel, this change in the continents sets up fluid veins in the contained blood, and the walls of the vessel are thrown into vibration thereby. Still, although this explanation is rational in itself, yet we may ask why it occurs in some anaemias and not in others? Again, why is it—as I think it is—incomparably more frequent in chlorosis than in other anaemias? In my experience it is not usual to get the venous hum in plumbism, in malaria, in cancer and so forth; it may be there, but it is not to be foretold, while in chlorosis
to foretell it is a fairly safe prophecy. Yet if it be true that in chlorosis the vessels are not empty as they are in some other anæmias, surely it is in chlorosis that the hums should be less, commonly heard. Perhaps the tone of the vessels enters into the causation. Moreover, there is an old hypothesis that the hum is due to the "thinness of the blood," the corpuscular contents of which as we know are notably reduced: this hypothesis has never received much countenance from competent judges; but Potain has brought it forward again on the basis of experiment. Potain so arranged a tube in connection with a reservoir that at one time serum should run down the tube, at another defibrinated blood containing the normal number of red corpuscles; on the use of the stethoscope the murmur was heard to fall in intensity when corpuscular blood replaced the serum. Whether this observation has been verified by other observers I do not know; if so, it has an important bearing on the generation of the bruit de diable. The hum, as I have hinted, is to be heard less certainly and loudly in other veins, in other kinds of anæmia, and even in some healthy persons. Many years ago in a foreign hospital I was told to hearken for a murmur on placing the stethoscope on the eyeball of a chlorotic patient; by this manoeuvre, which I have often repeated since, the hum, fainter than in the jugular, can be heard; but before we can say that it is generated in the cerebral sinuses we must be sure that it is not transmitted from the jugular through the bones of the face. Dr. Stockman tells me it may be heard sometimes over the torcular Herophili.

Cardio-arterial murmurs.—That a systolic murmur is not infrequently heard over the subclavian artery, especially on the left side and towards the outer third of the clavicle, is an old observation which has interested both elder physicians who have found food for speculation as to the modes of its causation and younger practitioners who have been alarmed by what they regarded as a sign of aneurysm. This murmur was carefully studied by the late Sir Benjamin Richardson, but I am not able at this moment to put my hand on the reference. Richardson named the murmur the "carpenter's murmur," as it is not uncommon in these and other labourers. To pursue this side of the subject would lead us into digression; but in chlorosis and other anæmias such systolic murmurs are to be heard in more than one artery. It is a matter of doubt, indeed, whether the systolic murmurs of obscure causation heard about the base of the heart in chlorosis are formed in the heart proper, or in greater or lesser part in the large vessels about the same region. Dr. Sansom offers the explanation that under nervous (vaso-motor) disturbance the arteries may be unequally affected in their calibre, some lengths being contracted, others dilated or of normal size; so that the blood passes from narrower to wider channels. If this be so, we are in possession of a vera causa, whether it be the actual cause or not. Richardson attributed the murmur in the subclavian, increased by manual labour, to the constricting pressure of voluminous muscles on the vessel; but as it may be heard in anæmic persons whose muscles are far from voluminous, we may find in Sansom's
hypothesis an essentially similar explanation. For in anaemia, not in chlorosis only, the murmur is to be heard in vessels, such as the carotids, not mechanically constricted from without as in muscular men the subclavian may be. The sound may be generated also in Graves’ disease. Sansom quotes from Roger a case in which this murmur was musical, audible at a distance from the body, and in every accessible artery of the body. No pressure of the stethoscope was needed to bring it out, and the persistent noise was a torment to the patient. It seems probable, then, that these sounds, like the venous hums, are due to vibrations of the walls of locally constricted vessels; and as they are but clinical curiosities we may not spend any more time upon them.

Certain murmurs heard in the region of the heart are of more importance. The humming-top sounds are little more than curiosities, as they cannot be relied upon even for diagnosis; but the heart murmurs, if such they be, may have a more serious signification. Physicians do not hesitate to say that some at least of the murmurs heard about the heart in chlorosis are mitral in origin, and significant of the deterioration of the cardiac muscles which we have already considered (p. 501). It seems clear, however, that more than one kind of murmur is to be heard in or about the chlorotic heart; and, if possible, these are to be distinguished, for some of them may be of a graver character than others. I am enabled by the kindness of Dr. Sansom to reproduce the useful diagrams published in his valuable work on the Diagnosis of Diseases of the Heart, wherein these problems are carefully discussed. The diversity of explanations of the cardiac murmurs of chlorosis, suggested by eminent observers, makes it difficult to treat usefully of the matter except from the mere phenomenal point of view; the moment we pass from phenomena to explanation we find ourselves not only in the midst of conflicting hypotheses, but also without any clue to a decision.

A precise appreciation of the phenomena is, then, our first duty. The murmurs to be heard in or about the heart are as follows:—(i.) First in frequency are the murmurs to be heard in the region of the pulmonary artery and conus (Sansom’s diagram, Fig. 27). In my student days all murmurs of chlorosis heard about the upper chest were indiscriminately referred to the aorta; to Walch, I think, we owed the closer description of these sounds with which we afterwards became familiar. All recent observers are agreed that the murmur now under consideration occupies the area delineated by Sansom; and Sansom says that it is “greatly influenced” by the posture of the body, being louder as the patient returns to the recumbent attitude. This reinforcement is largely due, no doubt, to the retardation of the pulse-rate. In this quality it is to be distinguished from the organic systolic murmurs most of which are less influenced by this change. Dr. Sansom quotes Handford (14) to the effect that this murmur again increases as the patient turns over to the right, and wanes as she turns prone on the face. It varies with respiration, but in no constant way. It is to be remarked that in these cases pulsation is often to be felt about the parts occupied by basic murmurs, namely, in the
second and third intercostal spaces, or even lower, and in the episternal notch. This we have all often observed and demonstrated at the bedside.

Fig. 27.—Area of pulmonary artery and conus, 50 per cent of cases. (After Sansom.)

Fig. 28. Area of right ventricle and conus, 11 per cent of cases. (After Sansom.)

Fig. 29. Area of aorta, 11 per cent of cases. (After Sansom.)

Fig. 30.—Systolic murmurs in pulmonary artery and at apex coexisting, 9 per cent of cases. (After Sansom.)

Fig. 31.—Systolic apex murmur only, 7 per cent of cases. (After Sansom.)

Now in respect of this pulsation we shall remember that in Graves' disease, where these pulsations are very evident, we also hear these
base or "pulmonary" murmurs, although the blood may present no change in the red corpuscles, either in number or colour. Sansom gives a very definite account of these murmurs; he says that in twenty-nine of his own cases murmurs over some part of the cardiac region were heard in sixteen; and in eleven they were in the pulmonary area. There is a large amount of evidence that similar murmurs may be produced by displacements of an otherwise normal heart: one such case I remember well in which, after death, the absence of all cardiac mischief was verified.

Arguments of weight seem to prove that these murmurs about the pulmonary area are not due to mitral regurgitation (Balfour), nor to pressure of a dilated auricle on the pulmonary artery (Russell, Handford). Dr. Sansom conjectures that the murmur is due to want of apposition of the mitral flaps on account of an enfeeblement of the muscular apparatus of the left ventricle. This is a modification of Balfour's surmise, and open to similar difficulties. I lean to the belief that the solution will be found in some altered relation between the blood and the walls of the vessels, especially the pulmonary artery and conus arteriosus; so that an excessive vibration of the walls takes place; if this be so, the cardiac murmurs, or some of them, will fall into line with the arterial vibrations of the same disease (p. 503) and with the venous hums. The pulsation of the vessels felt under other like conditions seems to lead us in the same direction. In Graves' disease this vibratile state of the great vessels is apparent enough.

(ii.) The murmur the site of which is indicated in Sansom's Fig. 28 need not detain us long. No doubt it is substantially the same murmur as the last mentioned, diverted a little in its area by incidental circumstances which may be guessed at rather than known. Sansom found it in eleven per cent of his cases.

(iii.) The next murmurs to be dealt with are those heard about the aortic region; that is, at the base (manubrium stornii) and at the second intercostal cartilage (Fig. 29). These murmurs are soft in quality and diffuse, not leading in any certain direction. Seeing that we were formerly taught that a murmur at the base is a common feature of chlorosis, it is curious to hear from Dr. Sansom that in his series this was the rarest of the chlorotic murmurs. From my own impressions I am prepared to coincide in his opinion. I have also noted that a murmur may be heard in this area as distinguished from that of the pulmonary region; the two, however, may coexist, and indeed may be mapped out separately. Within a few hours of writing these lines I have seen a case of chlorosis, mild in degree, in which, with the venous hum and some arterial vibration, a systolic murmur was heard at the second right cartilage and in the episternal notch. There was no trace of murmur in the pulmonary area. The history of the case, as a rule, will prevent any confusion between this murmur and a murmur of organic disease, whether due to rheumatism or to degenerative changes; and a persistently anaerotic pulse is decisively in favour of organic disease.

(iv.) Finally, there is the apex murmur in the region indicated in Figs. 30 and 31. This murmur was found by Sansom in sixteen per cent of his
CHLOROSIS

cases, and is a more serious matter, for it indicates mitral regurgitation; though in the cases we are considering the disorder is usually of a curable kind. There is no experience of the kind to which we may look back with more satisfaction than to systolic apex murmurs, which in their characters corresponded in all respects with those of permanent organic disease, but which disappeared entirely nevertheless. Loud or harsh murmurs in this place are not so common, if I may speak for my own experience, as the softer murmurs; still, soft or harsh, they arise under like conditions of atony, and to our repeated surprise—for repetition does not do away with the wonder of it—clear away altogether on appropriate treatment. These murmurs, indicative of mitral regurgitation as they probably are, I have frequently heard in middle-aged men who have indulged too freely in the pleasures of the table; men who show perhaps a little sugar in the urine for a time, or other such sign of slackened health. The like murmur arises in Graves' disease, in pernicious anaemia, after haemorrhage in childbed, and so forth. A certain lecture, published by Dr. Donald MacAlister in 1882, seems to me to throw light upon this subject. "If an animal be bled till it is feeble," he says, "a murmur indicative of regurgitation from the ventricle is heard with the heart sounds. You may inject proper salt solution to make up the normal quantity of circulating fluid, but still the regurgitation occurs. As the animal makes blood again, so that its muscles are properly nourished, the murmur disappears." On the clinical side such instances are to be culled on all sides from medical records; some of those recorded by Dr. Sansom, as progressing to dropsical and other systemic changes and yet to recovery, being among the most remarkable. Dr. MacAlister gave in his lecture what seems to be the explanation of this phenomenon; and about the same time he showed to me a small cast of the interior of a heart in systole which carried conviction on the face of it. Relying in part on his own observations, in part on those of Ludwig and others, Dr. MacAlister demonstrated the large part taken by the auriculo-ventricular muscular structures in closing this orifice during the systole. On inspecting the model, one began to wonder whether valves were not luxuries rather than necessaries; for the sphincter fibres, contracting during the systole of the ventricle, seemed to reduce the orifice almost to an imperceptible chink. This of course is not quite the case, for Hess has shown that the amount of reduction thus attained is only about one-half of the expansion area. We have, then, to call in the known factor of muscular atony in anaemia to explain that mitral regurgitation is very likely to take place; the relaxed muscle fails to do its share of the work, and the valves cannot quite make up for the defect. Moreover, we know that the papillary muscles are among the first to suffer in impoverishment of the blood, and that in those cases of anaemia which, by their severity, bring the patient to the post-mortem table, these parts, vital as they are, are found in states of more or less fatty degeneration. It is reasonable to assume, therefore, that these muscles are slackened. The difficulty is to understand why dilated hearts occurring in elderly folks and under other cognate conditions are so often unattended by a systolic murmur.
In the section on Mitral Stenosis in the following volume Dr. Sansom will discuss the coexistence of chlorosis and the former disease. In this connection I have only to suggest that as both of these diseases are found especially in women a large proportion of coincidence must be allowed for.

Potain endeavours with much ingenuity to prove that the murmurs of anaemia, or the chief of them, are of pulmonary origin. It is impossible to do justice to Potain's views in this place, and the advanced student is referred to his memoir (39). Sewall states that all "non-organic" murmurs at the base of the heart can be stopped by pressure with the stethoscope.

Edema of the ankles and feet is often very considerable in chlorosis, and occurs earlier than in other anemias; as, for instance, of phthisis or cancer, when it is a sign of dissolution. In chlorosis it seems to bear little relation to the apex murmur, which may be present or absent. This subject is more fully and broadly discussed in a later article, on Dropsy. Although, as I have said, recovery may be anticipated with some confidence from these conditions, attended by murmurs, and even by further evidence of cardiac failure which up to a certain point we may regard as transient, it is an interesting point to decide when the murmurs and other symptoms indicate more than a dynamic change—when the heart disorder has entered upon an altered static phase. The hope of complete recovery need not be bounded by the appearance of dropsy: in many cases I repeat that all such symptoms have passed away entirely. I remember having a serious difference of opinion with a medical man whom, unfortunately, I had no opportunity of meeting personally, in respect of a case of chlorosis in a young lady in whom a mitral murmur was audible at the apex, and in the axillary and subscapular regions. Her own medical man had assured the parents that the chlorosis was but a subordinate matter, and a permanent heart disease the principal evil. For this malady she was put under conditions which were not in all respects good for the anaemia, including the mental distress thus entailed on the patient and her friends. I did my best to root out this disheartening prepossession, but with little immediate success. However, I accidentally heard, a year later, that the subject of incurable heart disease was playing lawn tennis vigorously at all the parties in her neighbourhood. Yet I would not lead the unwary reader to mistake, let us say, the anaemia of insidious acute rheumatism, with heart lesion, for chlorosis with but a temporary relaxation and dilatation of the structures about the orifice.

Hypoplasia of the blood-vessels has been discussed already, and for a fuller account of these phenomena the reader is referred to the articles hereafter on "Congenital Malformation of the Heart" and "Diseases of the Arteries."

Thrombosis.—A remarkable and painful feature of some cases of chlorosis, happily rare, is the tendency of the blood to form thromboses in the cerebral sinuses, and indeed in other vessels of less immediate importance. Thrombosis may occur in such a vein as the femoral, or it may occur in the longitudinal or other cerebral
sinus. Professor Osler quotes a case in which chlorotic thrombosis occurred in the axillary artery, with the consequent loss of the thumb and part of the fingers. The symptoms of thrombosis of the cerebral sinuses are dulness, stupor, vomiting, dilated pupils, delirium, and occasionally double choked disks. In a case under the late Dr. Bristowe tenderness and swelling of the right internal jugular vein appeared. This was followed by thrombosis in the right leg, yet the patient ultimately recovered. I have a vivid recollection of a similar case in the Leeds Infirmary in a servant girl of some twenty years of age. In other cases, of which I also remember one, hemiplegia may occur, and cases of this accident in chlorosis have been published by many observers. In thrombosis of the sinuses there is no palsy. Dr. Coupland says that this thrombosis does not occur in pernicious anemia [art. "Pernicious Anæmia," p. 519]. Reference to cases of thrombosis will be found in the list at the end of this article, and in Professor Welch’s article on "Thrombosis." Twice I have been much pained to hear of the sudden death from this accident of patients concerning whose ready recovery of health I had expressed myself confidently but a few days before.

Phlebitis, especially in the legs, is no very rare event in chlorotic women, and it is said to be more often bilateral in them (39, 43, 6, 41). It occurs in grave cases of chlorosis, and has been attributed to fatigue and chill. Its progress is usually rapid, and, accidents apart, the prognosis is very favourable.

Genito-urinary system.—In some cases of chlorosis the pelvic organs, like the arterial, are found ill-developed—the uterine hypoplasia of Virchow. It is difficult to believe that these cases are ever cured by medical means, or by any means. They find their way into the museums of pathology. Amenorrhoea is of course a feature of them.

Amenorrhoea is also usual in ordinary chlorosis, though it is far from invariable. Amenorrhoea is not only the ordinary condition, but also the most advantageous; indeed, it may be called the protective side of the process. If I may speak from a few examinations, I would say that in the cases of chlorosis in which the red corpuscles are numerically much diminished (say to 3,000,000 or under) menorrhagia or even menstruation in normal quantity (which is a relative menorrhagia in such persons) is or recently has been present. I find that Sir R. Gowers has observed falls of 10 to 20 per cent in the number of the red corpuscles after a menstrual period. These cases are less easy to cure. I need not say that many chlorotic girls are brought to us in order that the menses may be recalled; and we have to explain to the friends that if, by local and specific means, such an achievement were possible, the step would be rather a misfortune than a blessing. As an old medical friend of mine used to say to troublesome mothers, "Madam, when the works are put in order the clock will strike." In chlorosis a very slight loss of blood will intensify the impoverishment of the blood beyond all expectation.

Chlorosis may appear before menstruation has ever shown itself. Stockman in 63 cases found menstruation scanty or irregular in 29,
absent in 12, normal in 4, profuse in 10. Three girls (aged 13, 15, and 19) had never menstruated, and in five no note had been made (normal?). Leucorrhoea is not infrequently complained of, and is cured by the iron. Of the urine I have already spoken; it is as a rule poor rather than loaded by products of waste, whether normal or abnormal. In particular there is an absence of those elements, such as indican and the conjugate sulphates, which would signify excessive fermentation in the intestines and absorption of toxins into the circulation. In pernicious anæmia the urine, like the skin, is usually darkened by the presence of urobilin in excess.

Nervous-muscular system.—Girls and young men alike, as they are adolescent, often go through phases of temper which are a source of anxiety to their friends; more new impressions, more new desires crowd in upon them than they can set in due order and subordination. It will not do, then, to put down the caprices, passions, perversities, and apathies of this season of life to any one of its disorders. They may occur even in the healthiest of both sexes; and with a little patience and protection from folly will “defeate to a pure transparency.” Yet chlorosis has, no doubt, some fretfulness of its own; lassitude and irritability meet together, and are due to want of activity in the nervous centres. There is no staying power; and although there may be proteids enough for repair, a small quantity easily provided of an element in which chlorotic blood is not deficient, yet the oxidation of carbohydrates and hydrocarbons for the supply of energy is behindhand. Fatigue products, also unoxidised, accumulate in the muscles. Dr. Sansom is disposed to attribute the fatty and other degenerations of the heart to a direct influence from the nervous system; at any rate we see irritability and loss of control (inhibition) in those higher centres which are the last to develop and the first to feel the lack of good blood. With these perturbations neuralgias are common, especially the neuralgias of the face, and headaches—frontal, temporal, or vertical. Gastralgia and pain under the left breast are common troubles of the chlorotic; the latter often coexists with leucorrhoea and disorderly heart, and with hysteria. Dr. Head has shown that all referred pains, with their accompanying tenderness, are apt to spread widely under the influence of anæmia. Thus widespread “neuraltic” pain and superficial tenderness may, in anæmia, be due to some simple cause. In the same way the headaches so common in anæmia are, in the majority of cases, a true referred pain, accompanied by tenderness, and correlated with pain and tenderness of a like nature on the chest or abdomen, according to the laws he has laid down. In a certain number of cases the headache and neuralgia represent a widespread pain referred from some organ of the head, such as the eye or the teeth. In extremely few cases, apart from pernicious anæmia and its allies, is the headache directly originated by the anæmia, though its wide distribution and prominence as a symptom are due to this cause. Certain kinds of palsy have been indicated under the circulatory system.

Optic neuritis is discovered occasionally in chlorosis; but the nature
of its association with this malady is wholly unknown. Sometimes it appears rapidly as a papillitis, as in many cases of tumour. The prognosis is probably favourable: I have never come across an instance of permanent injury to vision in this kind. The sign may, however, embarrass the diagnosis, especially if headache be present. Choked disk may be seen in cases of thrombosis.

Diagnosis.—The chief difficulty in the diagnosis is to distinguish chlorosis from other anæmias, simple or toxic. Gilbert lays much stress upon the doctrine that upon chlorosis this anæmia or that may be superposed, or that two kinds of anæmia may be associated from the first in one person. Dr. Lloyd Jones also points out the same difficulty. If this be so, and there is strong reason to suppose that thus it is, the diagnosis in a given case of chlorosis may be no easy matter. We have seen that chlorosis is more than a simple anæmia following with uniformity on the withholding of blood, and menstruation, unfavourable conditions of life or work, or lactation may "superpose" a simple anæmia on the chlorotic (chloro-anæmia). I have suggested that such may be the compound causation of those cases of chlorosis in which the number of red corpuscles is very deficient (3,000,000 and under). A further difficulty, and a far more important one, lies in the possible confusion between chlorosis and such toxic anæmias as plumbism, rheumatism, chronic Bright's disease, syphilis, arsenic poisoning, and so forth. Of all these puzzles we see striking examples. One young lady, with a green pale face and menorrhagia, presented on closer examination a blue line on the gums. In the drinking-water lead was found in considerable quantities. In another such case, one which resisted all treatment, after a protracted search for some external cause, we discovered arsenic in large quantity in the green unsized*wall-wash of her own sitting-room (not a paper). On the removal of this wash the symptoms gradually subsided. Syphilis does not give us so much trouble in women as in men, but is not to be forgotten. The quick effects of its specific remedies may betray syphilitic anæmia and place the diagnosis beyond doubt. Rheumatism is often insidious in young people, it is a potent cause of anæmia, and its murmurs more than "dynamic." To the anæmia of malignant disease I need not refer; I do not remember any difficulty in such cases. But in chronic Bright's disease in young persons I have not infrequently felt a brief indecision. The touch of the pulse will in all probability put the observer on the right line, and an examination of the retina and of the urine should settle the diagnosis. It is stated by some authors, as I have said, that a pulse of high pressure is apt to arise in chlorosis; this may perhaps occur in constipated patients. However, an examination of the urine will rarely fail to indicate the correct diagnosis.

The anæmia which precedes the appearance of pulmonary phthisis may create embarrassment in some cases; the absence of murmurs may guide us more or less, and the thermometer may come to our assistance. Dyspepsia may accompany any anæmia; there is nothing
characteristic in 'the dyspepsia of chlorosis; and if an organic murmur be also present we may find it impossible to arrive at a certain diagnosis without delay. Fagge published a case from the records of Guy's Hospital, in a girl of 18, in whose case the diagnosis of chlorosis was upset on the post-mortem table; a large caseous mass of tubercle was dislodged from the cerebellum, and a few scattered tubercles were found also in the lungs. The blood was not systematically examined in those days (1861). The specific bacilli cannot be found in such cases.

For the diagnosis between chlorosis and splenic anaemia, a disease of the "chlorotic type," the reader is referred to the following article on this latter subject.

Anchyllostoma, we are told, produces a state not always to be distinguished from chlorosis, not even by examination of the blood. The blood in anchyllostoma, however, is generally said to present the characters rather of pernicious anaemia than of chlorosis. Pernicious anaemia is more readily to be distinguished from the latter by the blood, with the aid, perhaps, of the thermometer, and of an examination of the urine (vide art. "Pernicious Anaemia," p. 519).

Addison's disease might give us pause for a while. I remember one such doubtful case in a young woman; but even in the absence of pigmentation a careful survey of the symptoms and history of the case should preserve us from error.

Prognosis.—Chlorosis has never seemed to me to be the obstinate disease that it is for some writers. I may have been fortunate in not meeting with bad cases of it; still, although my experience of chlorosis has chanced to be exceptionally large, I recall few cases which seriously resisted treatment. The danger is lest the disorder relapse time after time. How this is to be prevented we shall consider in the subsection on treatment.

Prof. Stockman tells us that of his 63 cases 27 were in the first attack, 11 in the second, and 22 had suffered from more than two attacks. Many of these, he adds, did not persist in the remedies ordered for them, and became chronically anaemic. Some persons relapse in spite of all care; their blood is perpetually unstable, and iron is a necessary aid even in middle and later life. Dr. Stockman estimates the time of apparent recovery at four to six weeks. This period will be considered more fully under the head of treatment.

I find myself at some disagreement with those who say that phthisis is to be feared as a sequel of chlorosis. It is impossible to be assured that a patient weakened by chlorosis, or by any other malady, will not fall into phthisis; yet in my experience this sequel, far from being a common result, is indeed somewhat rare. It may be that the "prephthisical anaemia" has been occasionally mistaken for chlorosis. Gastric ulcer is more to be feared, though the causes of its association with chlorosis lie in obscurity. Of apoplexy and thrombosis of the sinuses I have already spoken. Happily they are events too rare to enter into ordinary forecasts. I repeat that the thing to be feared is relapse after relapse of the chlorosis itself. No careful prognosis can be given
without repeated examinations of the blood. It is more than possible that many cases of chlorosis recorded as aberrant or peculiar were not cases of chlorosis at all.

Treatment.—I may almost paraphrase the words of Professor Osler in respect of quinine and malarious fever: "The physician who cannot treat chlorosis successfully with iron should abandon the practice of medicine" (vol. ii. p. 742). Physicians who restlessly turn from one preparation of iron to another, and from one drug to another, in order to find a cure for unmanageable chlorosis, must meet with peculiar cases. It is only by a strong effort of memory that I can recollect any cases of chlorosis in persons of common sense and reasonable obedience in which iron failed to effect a cure. On the other hand, I have had many cases submitted to me as intractable in which, if time and opportunity were favourable, there was no difficulty in compassing a cure. How are we to explain the failures? The reasons may be two: first, that iron failed of success because given in insufficient quantity; and, secondly, that the treatment was not continued long enough to counteract the strong bent to relapse which is seen perhaps in all cases more or less, and in some most doggedly. This latter reason covers, I suspect, most cases of failure. It is well never to begin to treat a case of chlorosis without telling the patient that the first course of medicine will extend to no less than three months; and that for a year thereafter she must be re-examined, and in all probability submitted to further courses of ferruginous tonics, as the signs may indicate. In all cases of severity the blood should be examined regularly, and this process has the incidental advantage of keeping the importance of the matter before the patient's eyes. During the first two or three weeks of ferruginous treatment the red corpuscles will rise quickly to the normal standard in number; though not in size, colour, or vitality.

It has been said of late that the first change to be seen is an increase of white corpuscles, and that these bodies act in some way as carriers of iron to the red. The manifold conditions on which the increased apparition if not the increased generation of white corpuscles depends are so little understood that we cannot be sure when an afflux of them is other than incidental.

The numerical increase of red corpuscles gives rise to a sense of relief often so rapid and so great that the unwarned patient jumps to the conclusion that she is "all right again"; and may throw medicine to the dogs. If so, the case may well be an "incurable" one. The increase of hemoglobin, and the attainment of full growth by the corpuscles—which are the essential elements in recovery as are the reverse processes in falling ill—take place much more slowly. It is no uncommon thing to find that a return of hemoglobin to the normal standard takes as long as three months; and for this reason three months should be enjoined as the shortest time in which a cure is to be completed. Even then relapse is more common than not. When I began practice, iron was given in doses too small to effect a satisfactory amendment, and gradually it became
apparent that larger doses are required. Now there is a reaction, and
physicians are saying that smaller doses suffice. My own opinion is that
in cases of any severity, if recovery is to be ensured, iron must be given
with a liberal hand; the quantity of the metal is more important
than the particular preparation. Without returning to what has been
aid concerning the mode of operation of iron in chlorosis, I may
emind the reader that, although in anemia of simpler kind, as for
instance after a hemorrhage, "food iron" is adequate to bring about a
repair, the iron given in medicinal doses in chlorosis must certainly have
some further effect than the mere replacement of that required to rebuild
the hemoglobin; it must have some stimulant, tonic, or "specific" action
which conspires to the same end. A few grains of the ammonio-citrate
of iron is not a dose to cure chlorosis of any severity; far more than
this may be needed. It is my custom to use the sulphate of iron alone,
or with aloes, in the form of pill. The addition of an alkali to the
iron is quite useless, and by making the pills more bulky is in-
convenient. I generally administer one grain of the sulphate thrice
daily after meals for the first week, two grains in the second week, three
grains in the third; it is rarely necessary to go beyond this, though some
patients do not respond till five-grain doses are reached; this, however, is
exceptional. When the dose of three grains is reached, I direct that this
quantity—nine grains daily—shall be continued for two months; the
dose is then reduced by a grain, and thus administered for a fortnight;
them one-grain doses are ordered for a month. During this time the
pulse is probably settling to the normal rate, and if for a month before the
end of this course the hemoglobin has been constant at the normal
standard a relapse is not very likely to occur; though of course the
disorder may reappear after a time from the original causes. Recently
I came across some little lozenges containing iron, called "jelloids."
These I have found very successful, partly no doubt because being
convenient and palatable, and arousing no fears of injury to the teeth,
they are taken regularly, partly because they retain their free solubility.
Occasionally the sulphate of iron causes some gastric irritation, the
"jelloids" seem not to do so. I have often suspected that incurable
chlorosis may mean insoluble pills; pills made up, for instance, with
gum tragacanth and the like become as hard as pebbles and about
as useful to the patient. For the flushed chlorotic patients (p. 498) the
laxative iron mixtures are indicated, such as the combinations of tincture
of the perchoride with sulphate of magnesia; or of equal parts of Griffith's
mixture and compound decoction of aloes, a most efficacious medicine and
not so nasty as it looks.

It was an imposing lesson of our youth that iron is not to be given
till the patient is "prepared" for it; and to this end bottlefuls of soda
and gentian, and so forth, would be prescribed; far be it from me to
encourage a careless mode of administering any drug, yet nevertheless I
think this so-called preparation was otiose and even mischievous in so far
as it wasted time. I rarely find such preparatory courses necessary. If
the tongue be white and sticky and the bowels constipated let a blue pill and a dose of salts be given; this done, begin with the iron, and watch the remainder of the tongue-cleaning process going on fast enough under the iron. The dyspepsia being in most instances the consequence of the deprivation of oxygen, the assimilative changes will improve, without any direct attention, as the hemoglobin is restored. In exceptional cases, no doubt, some precautionary measures may be desirable; of these the physician will judge.

I have tried all or most of the so-called preparations of "organic iron" produced for us by our excellent allies the manufacturing druggists; helpful as many of their novelties are, I regret to say that "organic iron" does not seem to be one of them. Perhaps I may make an exception in favour of an old-fashioned French solution of malate of iron which I have found that patients with queasy stomachs can take when ordinary ferruginous drugs are ill borne or seem inappropriate. Gilbert has found the protoxalate very useful; it is said to be soluble in the gastric juice. Stockman indeed says that "inorganic iron" is more rapidly effective than "organic iron."

Of "adjuvants" teachers and friends recommend many to us; ether, liquor ammoniae acetatis, nux vomica, and so forth: but I cannot say that I have found in any of them more advantage than such as may flow in the individual case from the ordinary properties of these accessories; they may be needed or they may not, usually not. It is well, however, to add some cordial such as chloric ether or sal volatile to all steel mixtures.

On pathological grounds much has been made of late of an antiseptic treatment. In a paper lately read at Cambridge by Dr. Latham, great stress was laid by the author on the value of the liquor of the perchloride of iron, because, as he showed at the time, it contains much free chlorine. Dr. Latham's claims on behalf of this vehicle of iron are probably well founded, as they are in accord with other observations of the kind. For instance, Townsend thus tabulated his results in 87 cases:

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgbm. mere.</td>
<td></td>
</tr>
<tr>
<td>β-naphthol (30 cases)</td>
<td>1:85</td>
</tr>
<tr>
<td>Bland's pills (31 cases)</td>
<td>5:07</td>
</tr>
<tr>
<td>Naphthol first and afterwards Bland's pills (12 cases)</td>
<td>6:70</td>
</tr>
<tr>
<td>Bland's pills alone (19 cases)</td>
<td>4:50</td>
</tr>
</tbody>
</table>

This table shows a decided advantage in favour of the use of β-naphthol before the pills; and in another such series, of 28 cases, the Hgbm. increase was 7:9 per cent. In the Boston Medical Society, to which this paper was read, it was generally agreed that intestinal antisepsis combined with iron gives better results than iron alone.

I remember in a few cases, when for some reason the iron did not take good hold at first, the drug seemed to get a start on the addition of arsenic or phosphide of zinc; ordinarily to treat chlorosis with these drugs is, to say the least, a waste of time.

In the belief that in chlorosis the volume of the serum is increased
(serous plethora), bleeding and diaphoresis have been recommended as means of cure. It is not apparent how an operation which reduces the number of the red corpuscles can be otherwise than injurious. However, Schmidt treated and tabulated the following eight cases (a "bleeding" was 80 ccm.): —

<table>
<thead>
<tr>
<th>Case</th>
<th>Average incr. Hb, per cent.</th>
<th>Weekly incr. of weight in kilos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>i. One bleeding and iron</td>
<td>6.20</td>
<td>0.73</td>
</tr>
<tr>
<td>ii. Iron alone</td>
<td>6.18</td>
<td>0.48</td>
</tr>
<tr>
<td>iii. One bleeding</td>
<td>2.50</td>
<td>0.92</td>
</tr>
<tr>
<td>iv. Several bleedings</td>
<td>0.59</td>
<td>0.51</td>
</tr>
<tr>
<td>v. Sweating cure</td>
<td>0.59</td>
<td>0.44</td>
</tr>
<tr>
<td>vi. Bleeding and sweating</td>
<td>0.36</td>
<td>0.46</td>
</tr>
<tr>
<td>vii. Several bleedings, sweating, and iron</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>viii. Several bleedings and sweatings; no iron</td>
<td>0.56</td>
<td>0.19</td>
</tr>
</tbody>
</table>

The good effect in the first case was entirely due, no doubt, to the iron.

While prescribing pharmaceutical remedies the physician will not forget, so far as in him lies, to rectify such disadvantages of life as he may be able to ascertain. Over-pressure at school, unwholesome conditions of work or amusement, late hours, worry, tight lacing are points to which his attention will be directed; yet while relaxing overwork, if any, he will be no less alive to the evil of idleness or desultoriness. As much time as possible should be spent in the open air and in such gentle exercise as the strength and respiratory functions will permit. Quiet horse exercise or cycling may be encouraged, and some course of study likewise which shall interest and discipline the mind and temper without fatigue. The patient should sleep, if possible, with the bedroom window open; if this be prevented by hard weather, the door must be open. A cold bath will probably prove more than the deficient heat production can support, but the rapid application of the wet sheet can usually be prescribed with advantage; this is better done in the forenoon two hours after breakfast, and, during the colder months, in a room with a fire. Excessive cold, as we see in hemoglobinuria, seems to destroy the red corpuscles. If love affairs harass the patient it must be remembered that marriage is no direct cure.

I have said that the deficient powers of heat production often forbid too bracing a line of treatment; in a bad case of chlorosis, one in which perhaps iron is not telling at once, the dissipation of heat and the expense of muscular activity must be husbanded by a week or a fortnight in bed. Such a measure often gives an impulse to the curative movement, and proves to be an economy of time in the end. The facial, gastric, and other neuralgias, which may be prominent symptoms of the case, are usually relieved at once by this simple means. A farther reason for recumbency is given by Dr. George Oliver in his interesting little book on Pulse-Gauging.
Thus the calibre of the arteries is enlarged, residual blood in the ventricles is reduced, and dilatation of the heart is prevented or relieved. By his arteriometer Oliver finds (p. 135) "that from 25 to 100 per cent more blood is discharged into the tissues in the recumbent than obtains in the sitting posture... the radial calibre... increases in recumbency, as a rule, in proportion to the severity of the anemia and to the need of recumbent rest." As soon as the appetite improves and the other graver symptoms begin to give way, change to the seaside or to the hills may be advised; but cold, I repeat, is injurious in chlorosis, and at considerable altitudes the deficiency of oxygen would be more and more sensibly felt.

It only remains now to say the few words which are necessary on the diet of chlorosis. It is of the first importance to overcome the common distaste for meat. Girls will say that the entry of a dish of hot meat into the room makes them feel sick; kindly and gradually this aversion must be overcome, and meat must take its due place in the diet. Eggs and milk if well digested will be included, and sweets and other kickshaws discouraged. Green vegetables are said to be useful for their chlorophyll, at any rate they avert constipation. It is desirable, if a fair meal be taken, that nothing be offered between meals. We are pointedly asked in these cases of chlorosis whether alcohol in any form is to be prescribed. Of itself I believe that alcohol is of no direct service. It is possible now and then that a bad appetite may be coaxed into more activity by a glass of stout, or of red wine and water; if so, the use of these aids is justified. Some young persons dislike pure water; and indeed it is not well for these chlorotics to drink much with meals: half a tumbler of milk may be the table drink, and three hours after meals a glass of hot water will act beneficially both on the stomach and on the secretions. Careful mastication of the food is of great importance.

In conclusion I would repeat that to test the blood not only for the number of red corpuscles and apparent hemoglobin value, but also to ascertain whether they are equal and of full size, is the only trustworthy means of gauging the rate and degree of cure; a lowered pulse-rate, however, is a sign of amendment, as is reacceleration of impending relapse. Colour generally returns to the face and steadiness to the breathing long before the cure is established.

T. Clifford Allbutt.

REFERENCES


T. C. A.