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SEX HORMONES.*

by

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The glands of humans and mammalians may have an external secretion or they may be ductless, having only an internal secretion into the circulating blood, or they may be a combination of the two varieties, one portion secreting externally and the other internally. This is the case with the pancreas and the germinal glands. The external secretion of the gonads has been well known for a long time. The internal secretion of the testicles was first inferred by Brown-Sequard; in the case of the ovary it was proved by Knauer and Halban (Vienna), who made the first transplantation of the ovaries, with the effect that in the guinea pig, the usual atrophy of the uterus following castration did not take place and in apes menstruation continued normally. This effect could only be produced by the secretion of some substances into the blood. The part of the ovary for external secretion undoubtedly was the *Graffian follicle*. Prenant (Nancy) and Born (Breslau) presumed the *corpus luteum* to be a ductless gland. You see here its structure and may judge for yourself, that there is no other gland in the body more obviously constructed for internal secretion than the corpus luteum.

A few hours after the ovum leaves the ovary, the ruptured follicle changes into the corpus luteum. You see here the *big succulent, red organ. In the cow* it occupies almost the whole ovary. In cases of pathological pregnancy, e.g., very often in ectopic pregnancy, you see a cystic degeneration of the corpus luteum; in hydatidiform mole and also in chorionepithelioma a much larger, poly-cystic corpus luteum is nearly always seen. Chorionepithelioma, which I was the first to describe, arises from the epithelium of the chorionic villi and is preceded in 50% of cases by hydatidiform mole. This was the reason why Marchand and I independently investigated the hydatidiform mole.

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* Read before the Hong Kong University Med. Society on 17th February, 1936.

[We regret that we are unable to publish the excellent slides and pictures with which Prof. Fraenkel so ably illustrated his lecture.—Ed.]

formerly mistaken for a myxoma by Virchow. We found extensive proliferations of the epithelial layers of the villi. The grape-shaped distension of the connective tissue was mucous, not myxomatous, it is of a secondary, degenerative nature. In cases of hydatidiform mole and chorionepithelioma you always have a cystic degeneration of the corpus luteum, further you find an expansion of luteum cells and cysts over the whole ovary. When the mole of the tumour is eliminated, these cysts and luteum cells disappear spontaneously. Even if the corpus luteum does not undergo cystic degeneration, but is only compressed by an ordinary ovarian cyst, pregnancy is arrested. Furthermore if you perform a unilateral ovariotomy in pregnancy for an ovarian cyst, no harm comes to the ovum if the corpus luteum is present in the other ovary. But almost invariably the ovum is lost, if the corpus luteum is removed. After bilateral ovariotomy Polano and I saw "dry retrogression" of pregnancy without abortion. The ovum wrinkles, shrinks and dissolves without haemorrhage and without discharge. Moreover, in cases of sterility, especially in the cow, you very often find cysts of the corpus luteum. After the veterinary surgeon has ruptured these cysts through the rectum, the cow comes on heat and the sterility is overcome. From all these examples you see that there must be a connection between the corpus luteum and the ovum. It is however not only a question of the relation between the corpus luteum and the ovum, but also between the corpus luteum and the uterine mucous membrane. The mucous membrane of the uterus in the absence of the corpus luteum persistens or a corpus luteum cyst, presents this curious appearance of the mucous membrane. In pregnancy when the corpus luteum is fully matured, the uterine mucous membrane in the neighbourhood of the ovum has this structure. When the corpus luteum has been formed and cohabitation has taken place with a vasectomised buck, or when instead of the ovum you introduce a foreign body into the uterus, which has previously been well prepared by a fresh corpus luteum, then you have the appearance found by Bouin and Loeb shown in this figure. As everything seemed to suggest an internal secretion of the corpus luteum, I assumed that its effect would consist in a remote influence on the mucous membrane of the uterus and the impregnated ovum. Following this line of thought I began my experiments.

Knowing some facts of animal sexual physiology it was easy to verify this connection. The rabbit ovulates only after copulation and receives the male only when ready for ovulation. Consequently the date of ovulation can be ascertained. After copulation one knows that the impregnated ova take 5 days to reach the uterus. Mandl and Schmid had made use of this knowledge when trying to produce extra-uterine pregnancy. They interrupted the path of the ova by ligature of the tubes. I also experimented during the 5-day period, and although not interferring with the migration of the ovum, I destroyed or extirpated the corpus luteum during that period And behold! the ova could not implant themselves into the uterus, whereas in control operations the implantation always took place, if the corpora lutea were left intact. The same destiny awaited the ova already implanted when the corpora lutea were removed up to the 14th day of pregnancy, that is mid-term in the rabbit. The removal of half of the corpora lutea had no influence on the implantation or growth of any of the ova. The death of the ovum is followed by dry retrogression without abortion. The same intra-uterine disappearance even in human pregnancy was observed by Polano and myself after bilateral ovariotomy. Consequently the implantation and early development, so far as rabbits are concerned, depends on the corpus luteum. This was proved by more than 400 experiments with exactly similar results, and it has been confirmed by all later investigators. Comparative physiology through all the mammalian classes is still lacking but a collective investigation is being arranged by me through all cultivated countries. I was further able to show that the protection of the ovum is only one of the functions which are of the greatest importance in Sex Biology.

The main function is the cyclic transformation of the mucous membrane of the uterus, the attainment of the so-called stage of secretion, the cyclic increase and decrease of the organ and the secretion of substances which cause heat pregnancy as well as the inhibition of the ovulation: all this leads in the end to the menstruation of humans and apes. Even if there is no fertilized ovum, the process takes place in the same way; from the histological point of view the final result is the development of the decidua. This membrane is not only formed in pregnancy and pathological conditions (*endometritis exfoliativa*) but it can be found in all menstrual blood, even in the virgin, as was proved by my pupil, Linder. That the transformation of the mucous membrane and the development of decidua depends on the corpus luteum, has been proved by two more classical experiments. Now one can understand why Ancel-Bouin produced pseudo-pregnancy after copulation with a sterilized buck and Loeb was able to obtain decidua by introducing foreign substances into uterus of guinea pigs during the functional period of the corpus luteum.

I will now show you the development of the human uterine mucous membrane in a series of microscopic slides under the influence of the ripening follicle and especially the corpus luteum. You will agree, that nowhere else in the body, except in the uterus, can such important and extensive changes take place in so short a time. The work of observing and recording this periodical (or rythmical) change is to the great credit of two Viennese investigators, Hitschmann and Adler. I am afraid I have to confess that, knowing what only I knew at this time, about the hormonal functions of the corpus luteum, I should have been able to have anticipated this ovulation of the physiology of the uterine mucous membrane and to have undertaken systematic investigations in this direction. Now you understand the nature of the menstruation; it does not consist in merely a cyclic loss of blood, but in a cyclic discharge, which exists in all the mammalia and contains the substances necessary for the building up of the foetus: glycogen, trypsin, calcium, phosphorus, magnesium, arsenic, etc., substances, which are useful for the growing organisms but are poisonous if accumulated in the mother. There is a kind of "unwell period" for the woman so long as the poisonous substances remain in the body, and a sort of "monthly cleaning" when they are discharged. The haemorrhage in menstruation is therefore only of a secondary nature and unessential being caused merely by the tearing off of the spongiosa-septa. In animals with the exception of the apes, there is no menstrual bleeding, but a menstrual discharge or "menstrual equivalent", and the same is the case with women who suffer from underfunction of the ovaries.

Let us consider now, whether the corpus luteum is the only gland in the ovary with an internal secretion. We have shown previously, that its function is to produce the cyclic changes in the uterine mucous membrane, necessary for the embedding of the ovum. Before the first corpus luteum appears however, the young girl achieves a certain degree of maturity. The first ovulation takes place before the appearance of a corpus luteum. A young woman can become pregnant, without ever having menstruated. Consequently the internal secretion of the corpus luteum can neither influence the first ovulation which involves the growing, ripening and rupturing of the follicle, nor the first heat of the animal, nor the sexual desire of woman. We have to search therefore for a second internal gland. This was found by Bouin and Limon and called the interstitial gland of the ovary. My own investigations and those of my pupil, Anna Schaeffer, which extended over all classes mammalia, showed that this gland originates from atretic follicles. Not more than 1 in every 100, or 360 follicles out of approximately 36,000, ovulate and form copora lutea. Others remain in the primordial state, others grow up to half ripe follicles, others become atretic and still others lose the theca externa, and, uniting closely, from the lobes and acini of the interstitial gland partly with the necrotic ovum in the center. I did not find typical examples of the gland in more than half of 95 species of animals; in many there were only traces, or none at all. We would not find this so-called interstitial gland in typical form in man. Therefore, either its function is not constant or the follicle itself with its theca interna has the same potentialities as the well developed interstitial gland, or to define it more correctly, the totality of the growing follicles and the atretic and disappearing ones together form the interstitial gland.

Now let us look at such a gland, perfectly developed. Let us compare its structure with the corpus luteum next to it. You see the endocrine character of both. Both are without any efferent channel, both have cells filled with liquid granules, and are surrounded by capillaries, all this signifying the character of a gland of internal secretion. And yet there is a striking difference; in the corpus luteum there are large cells, full of protoplasm, a capillary network completely surrounding every cell, the most perfect example of a gland of internal secretion to be found in the body. Whereas in the interstitial gland the cells are small, the drops of secretion smaller and less numerous, and the capillaries surround columns and masses of cells, not each individual cell. The interstitial gland is less perfect; it is a more extensive endocrine gland. The corpus luteum is the gland of generation, appearing and disappearing once a month, guarding procreation, giving a rythmic impulse to the whole of the genital organs and even developing from the actual follicle, which has supplied the ovum.

The other follicles, having failed to achieve this particular culmination, unite anatomically and functionally with certain undeveloped structures of minor value, which are less typically gland-like, and undertake a function less extensive and not so strictly determinate but it functions over a longer period. They maintain the sexual function between two culminating points, acting vicariously until the next corpus luteum is ready, thus avoiding any possible interval. They are also of importance during the second half of pregnancy, when they become very hypertrophied; also before puberty and after the menopause, in neither of which, as we mentioned before, does a corpus luteum exist.

There is now ample chemical evidence for the truth of this primary theory of mine. Doisy and Butenandt discovered the active principle of the follicle and the interstitial gland. The latter established this formula. By exhibition of this hormone, heat can be produced experimentally i.e., the ripening of the follicle and the associated inclination to mate. The chemical structure of oestrin does not differ very much from that of the testicular hormone, as you see here: oestrin has only one benzene ring and between this and the next ring there is no methyl-group; but both the oestrus-producing hormones have the same elementary structure and each of them has a hydroxyl and a keto-group in the same part of the molecule.

Very different from these two, not only biologically but also in chemical structure, is the active principle of the corpus luteum, the hormone of pregnancy, formerly called progestin. That is without homologue in the male. Slotta and Fels succeeded in isolating the hormones of the corpus luteum in Breslau and discovered the following formula. These hormones are two very similar substances, called luteosterones. They are both di-ketones with a double bond in the first ring. The difference between them is in their melting-points and perhaps a very slight difference in the spatiate arrangements of the atoms in the molecule. These chemical facts were in the past year first established by Slotta and Ruschig in Breslau. A few months later Allen and Wintersteiner confirmed the statements of Slotta by investigations, which they had carried out simultaneously with and independently of

Slotta. Moreover Butenandt in Danzig and Fernholz in Göttingen proved the formula established by Slotta by synthesizing the hormones.

Now concerning the histological effect. Gorner was able to maintain pregnancy after extirpation of the corpora lutea only by means of concentrated extracts. Here we have then our really crucial experiment. The chemical relationship of oestrin (Theelin) to luteosteron is quite the same as the histological and histogenetical one of the interstitial gland to the corpus luteum. The chain of proof is complete and the part which the ovary plays in its entirety (interstitial gland and corpus luteum) is clearly defined. You will thus understand my satisfaction that it was in Breslau and in my own clinic that the hormones of the corpus luteum were discovered.

Evans, Allan and Smith, together with Zondek, acquainted us with the pituitary as the third endocrine sexual gland. Just as prolan from pregnancy urine stimulates the sexual function, implantation of the anterior lobe of the pituitary has a similar action, both produce their effects only if the ovaries are present. The follicular hormone causes similar but less marked symptons of heat, but it can also act in castrated animals. In this we have a substitution therapy, which acts directly upon the secondary organs, the uterus, the vagina, etc. Prolan and the implanted anterior lobe, however, merely through their stimulating influence on the ovaries, act indirectly on the secondary organs. Thus the pituitary is the superior gland governing the ovary, and extirpation of the pituitary stops ovulation and prevents pregnancy even when the ovaries are left intact. Later on we will show, that in some way the ovary is influenced by the other glands of internal secretion, but not in the same clear and dominating way as it is by the pituitary.

Let us look at the structure of the pituitary. Here we see the three well known lobes. The posterior lobe alone has no endocrine structure, although it supplies pituitrin, our best stimulant of muscular contraction. The middle lobe furnishes "intermedin" which was also analysed by Zondek and the anterior lobe furnishes several hormones, the most important of which are the growth hormone of Evans, the metabolism, the thyreotropic, the lactogenic and the gonadotropic hormone (prolan). The anterior and the middle lobes have the structure characteristic of glands of internal secretion and these two glands lie close to each other. Similarly in the suprarenal gland the medulla which produces adrenalin lies close to the cortex, which produces eucortone (interenalin)—a hormone absolutely necessary to maintain life, and besides, it helps to determine sex. Here again two important glands lie side by side in an apparently homogeneous organ. Another example is the pancreas. Still another example of this peculiar distribution of glands in couples is seen in the relationship of the thyroid and the parathyroid glands, both glands belonging to the branchiogenic system. For thyroxin we are indebted to Harrington; parathyreoidin is not yet properly isolated– when it is absent, tetany and disturbance of calcium metabolism follows. In the ovary also the corpus luteum and the interstitial gland lie quite close to each other thus producing the bi-glandular arrangements already described. This strongly suggests that the local connection of two glands of similar origin reappearing in 5 endocrine organs in the body is of the greatest significance.

The existence of a fourth genital gland is inferred; the placenta. If we demand a certain histological type for an endocrine gland, and apply this to the placenta we find the secretion transporting capillaries are very numerous, but secreting cells are missing. In the fully developed placenta, which contains large amounts of the hormone of the follicle and the corpus luteum, the foetal cells are very small and the only cells, which can be taken into consideration as possible for secretion are the decidua cells which are comparable with the lutein cells in their size and the quality of their protoplasm. Considering that the decidua is but a perishing organ, one could easily regard the placenta as merely a storing place for sexual hormones. Further the continuous supply of hormone after castration in pregnancy indicates the existence of still another gland producing the hormone besides the ovary. From the placenta Ehrhardt obtained corpus luteum—hormone in small quantities by a rather difficult method. By the way: Why is the appearance of the maternal side of the placenta smooth and shining although it represents an extended wound? The reason is, that the columns of spongiosa are merely glandular septa and are covered with epithelium. These lacerated septa lean against one another and so form an uninterrupted layer of epithelium, but when floated out in water, their structure can be well seen. Some authors speak of a fifth sex gland, the so-called myometrial gland of the uterus. Here you see it in the rabbit drawn on the 23rd day of pregnancy; Koiffer at Brussels first described it; I searched for it, again, through the whole mammalia. It is indeed a strange formation, but inconstant, even rare, and cannot be regarded as a gland of internal secretion, and the cells are not surrounded in a typical way by capillaries. I believe those large cells to be syncytial cells, which have migrated from the mucous membrane into the muscular layer. Froboese considers they are histioblasts. This point is of interest, as some authors believe, that the uterus itself produces an internal secretion, because postmenopausal symptoms may follow its extirpation. But those symptoms can be produced just as well by secondary disease, atrophy of the ovaries, or ligature of the ovarian blood vessels, or they are merely menstrual symptoms (molimina menstrualia), mistaken for post-menopausal symptoms. Later, when speaking of vicarious haemorrhage, I will discuss the difference between these two.

The correlation, synergism and antagonism, of the ductless glands is not yet completely understood. All the other glands of internal secretion with the exception of the ovary influence the constitution, metabolism, the circulation and the nervous system; like the heart, they are of general importance to the whole body. The ovary is different from all the others. The ovary has a particular function, which is precisely and easily definable: I will now explain to you this correlation and will begin with hyper—and hypo-function.

Where there is hyper-function of the ovary, all the other ductless glands are restrained. In all cases of diminution or absence of ovarian function, all the other glands hypertrophy. This is shown by the post-menopausal symptoms, which are merely symptoms of overaction of the thyroid, trembling, palpitation of the heart, the pituitary, adiposity, the suprarenal gland (flushes), etc. Consequently the ovary has an inhibitory influence on all the other glands. This influence however is not very strong, because in time after castration and the climacteric these symptoms are compensated. On the other hand in cases of dysfunction of the other ductless glands we always find the function of the ovary restrained, e.g., in myxoedema, exophthalmic goiter, acromegaly, dystrophy, diabetes and Addison's disease, sterility atrophy and amenorrhoea are the results. Consequently the other ductless glands stimulate the ovary; when they fail, the function of the ovary stops. The ovary on the contrary gives no support to the other glands when they fail—an unequal distribution in giving and taking. The ovary is inhibitory, whereas all the other glands of internal secretion hypertrophy and according to the degree of this hyperfunction we may have cases of special pregnancy-acromegaly,-hyperthyroidism.—Addison's disease or—tetany. This somewhat aloof position of the ovary can be illustrated by this diagram. Each of the other glands of internal secretion is a servant of the woman's own organism, maintaining her metabolism and her life. The ovary on the other hand controls the metabolism of the growing foetus. With its help the germ extracts ruthlessly from the mother all the substances it needs for its growth, and the hypertrophy and hyperfunction of the other ductless glands has to compensate this loss as far as possible by increasing metabolism. Thus the ovary in this sense is not for the purposes of the mother, but it is for the time being a foetal gland, conveniently housed in its mother's body. The ovary is, so to speak, the exterritorialised embassy or commercial representative of a foreign country, working not for the good of the host-country, but for the good of its home-country. None of the other glands of internal secretion governs a single organ or system of organs, but they mutually control constitution, growth, metabolism, respiration and circulation. The ovary, on the contrary, has a small and only inhibiting influence on these functions, but it governs one system only, and that alone. Without the ovary there is no sexual function. It is the gland of generation; it does not serve the individual; its function is the propagation of the species. This is the peculiar position of the ovary and explains its antagonistic attitude towards all the other glands.

VISITS TO THREE EUROPEAN SURGICAL SCHOOLS.*

by

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It has recently been my good fortune to visit three European Surgical Schools of note, namely, that of the University of Heidelburg in Germany, the Royal Infirmary of Edinburgh, and Guy's Hospital, London. I think the chief value of visits of the necessarily short type which one must of needs pay while on leave is not so much what one sees, in as it were glimpses, but the refreshment of sensing vividly the enthusiasm of the people who are making surgical history; and also the fact that when one subsequently reads any of their works, one has the tremendous stimulus of the personal contact and knowledge of their temperaments and an estimate founded on one's impression of their soundness.

Generally speaking, as a post-graduate, one only sees the technical ability of various surgeons. Their ultimate results in terms of the hard facts of mortality and improvement rates are closed books but honest folks do create a certain impression and atmosphere which one can only sense by meeting them: and one feels that what so and so says is probably true, and sadly sometimes one records in one's mind the probability that some one else is the type who will delude himself.

My first visit was to Heidelburg in March of last year, at the time when the students were all away on vacation. In Heidelburg the clinics are all run without the active participation of students who are entirely onlookers until after qualification when they have to do a recognised period of practical work before they are permitted to practise on their own. I was surprised to find that there were no organised schemes for post graduate work; but Professor Kirschner and his first and second assistants Drs. Zuchtnswerd and Peisler very kindly invited me to visit their operating theatres and ward rounds whenever I liked. I found my scanty knowledge of German a very great handicap especially on ward rounds, so I confined myself almost entirely to looking on in the operating theatres and was compelled to gather what information I could obtain almost solely through my eyes.

The first thing that impressed one, as is to be expected in Germany, was the orderly method and organisation. There never appeared to be a hitch. This was of course largely due to the facts that everyone taking part in the theatre work was well beyond the novice stage and the large number of people each with his or her definitely marked out sphere of activity. Nevertheless the smoothness of working and the consequent speed was striking.

* Read before the University Medical Society on 13th May, 1936.

Practically everything abdominal and below was done under spinal anaesthesia by the special technique devised by Professor Kirschner, who claims for it an unparalleled relaxation of the abdominal muscles and an almost complete absence of post operative lung complications. For an unusual degree of muscular relaxation I can personally vouch I saw a perforated gastric ulcer done, and the manner in which the anterior abdominal wall was lifted away from the viscera to make the roof of a cave into which one could look, and by suction clean, was very impressing.

Full details of the technique are given in the Journal of Surgery, Gynaecology and Obstetrics, September, 1932, and briefly it is done thus:—The patient is not given morphia before hand but just before the induction of anaesthesia, ephedrine is injected, the blood pressure having previously been taken, and is taken together with the pulse rate subsequently at 3 minute intervals throughout the operation and charted on a special chart.

Through a spinal puncture, about 15-20 ccs. of cerebro-spinal fluid are let out and replaced with 12-15 ccs. of air which makes a bubble in the theca, like that in a spirit level. Into the apex of the bubble is injected a mixture of percaine dextrine and alcohol which will not diffuse through cerebro-spinal fluid and so makes a localized sump in the lowered end of the bubble, which can be pushed up as high as necessary with more air. This anaesthetizes the nerves emerging from and entering the cord, so that a band of anaesthesia round the middle can be obtained.

On opening the abdomen the retro-peritoneal regions near the mid-line of the upper abdomen are infiltrated with novocaine to obliterate sensations via the autonomic nervous system.

If the patient during the operation shows signs of distress, scopolamine is injected, and any blood pressure collapse is combated with ephedrine and intravenous injections of glucose (5% in 1 pint of saline).

Professor Kirschner makes a point that this method of anaesthesia is one that requires much skill and experience and that in hands of the unskillful is dangerous. It is apparently not difficult to blow the charge up into the higher centres with drastic results. Great care must be taken to keep the head down below an angle of 25 degrees during and after the operation until effects have worn off.

I think the Germans are probably more suited to spinal anaesthesia than the less placid races. Certainly, I cannot picture English folk allowing themselves to be blind-folded for a spell before anaesthesia is commenced and during its administration as is done at Heidelburg. The German patients submitted to this, while in the ante-room for periods up to 20 minutes—and not under the influence of morphia!

In spite of the injection of novocaine as described, there was a considerable amount of discomfort and sometimes vomiting when the viscera were handled. However, there was remarkably little shock as indicated by the blood pressure during the operation. Subsequent happenings in the wards I did not witness.

Patients before operation are removed to a special ward near the theatre and are returned to it afterwards. So the sisters and staff are highly experienced in the pre-and post-operative treatment.

The arrangements and dispositions in the theatre were as follows:—Opposite the surgeon, stood two qualified assistants, the senior of the two directly opposite and doing the more important work while the junior attended to the cutting of ligatures, the holding of retractors and keeping the table clear of instruments which are taken, as soon as out of action, and dropped into a bowl at his side where they are gathered by a male attendant who sterilizes them and returns them to the larger of two instrument tables under the charge of a junior theatre nurse, who feeds a smaller table presided over by the theatre sister who stands on a stool, and who is head and shoulders above everyone facing the field of operation, and anticipates every instrument and ligature need of the surgeon, as well as directing the male attendant and junior nurse. This saves a great deal of time.

Usually, for clean abdominal work, rubber gloves are not worn, but when the peritoneal cavity is opened, thin white cotton gloves are used. This seemed rather like heresy in the land of origin of aseptic surgery.

Linen threads are extensively used for anastomosis of the intestinal tract and the instrument invented by Petz (by which double rows of aluminium clips are inserted) was used for closing off bowel in gastrectomies, etc.

Practically all cutting is done with a diathermy knife and smaller arteries are coagulated by touching the occluding forceps with the electrode.

An interesting instrument was a reservoir of local anaesthetic with a long needle attached. The anaesthetic in the reservoir was under pressure and flowed under the force of about 2-3 atmospheres on the release of a finger press button. One was reminded of a petrol "bowser" but its convenience was obvious.

With regard to individual operations, partial gastrectomies are remarkably frequently done for ulcers of the type and size which would in Britain most certainly be given the benefit of medical treatment. I was unfortunately not able to discuss their attitude to this question with them.

I saw one perforated gastric ulcer which had occurred in a young man about 18 hours previously. He was given a spinal anaesthetic as described above. The abdomen was opened by a mid-line incision, the ulcer closed, and the cavity of the peritoneum cleaned by means of a suction tube as thoroughly as possible in the condition of plastic peritonitis. A quantity of poly-valent serum prepared from organisms found in similar cases, was squirted round the cavity and the abdomen closed without drainage—which astonished me!

I saw Dr. Zuchtswerd transplant the ureters of a child of about 5 years for the condition of ectopia vesicae. He used the technique advocated by Coffey to the extent of having his text book handy. Incidently in the theatre there is a book stand; and books *are* consulted while in action. (How many times have I longed to have a comfortable anatomy book open near by when trying to sort out tendons and nerves of a lacerated wrist or something of the sort. I shall in future bring Gray into the theatre without qualms).

A dislocated semilunar bone in the wrist was treated by passing a Kirschner wire through distal ends of the metacarpals and applying traction for a week. This was not however, successful, and open operation was required. An old ununited scaphoid fracture was treated by open operation in which holes were drilled into the fragments, the fracture ends freshened and the wrist plastered.

Kirshner's system of extension with which you are all familiar, was of course largely used for fractures.

I saw one blood transfusion done. The blood was received into amber cups from a canula in the vein, transferred without any additions to an amber receiver from which the blood was forced by air pressure through a needle into the recipient vein.

An interesting case was a sub-acute obstruction due to a growth in the region of the splenic flexure. On exploration through a supra umbilical mid-line incision, it was decided that immediate extirpation was impossible so a small puncture was made in the transverse colon to relieve distension. The puncture was then oversewn and the transverse colon was sewn to the peritoneum to allow a small area to fill up a gap in the peritoneal cavity incision when it was closed. The remaining layers were then approximated, leaving a channel down to the exposed area on the wall of the transverse colon for opening later.

Professor Kirschner is working out a mechanical system for reaching the Gasserian ganglion with a small cannula into which a diathermy electrode is introduced to coagulate the ganglion. It consists of a stirrup which is fixed to the temporal region on each side by a screw with a rubber point. A second stirrup from the point of attachment of the first passes under the chin and an arm passes forward to the forehead from the second. A careful scheme of the various relations in distance on these three arcs has been worked out on thousands of subjects, and it is hoped that adjustments in terms of these relationships, will give the exact points along which the cannula can be pushed in a special channel. The system is not yet worked out completely as I saw two unsuccessful attempts.

Cystic goitres are very common in Heidelburg, and when necessary, operations on the thyroid gland are done under local anaesthesia.

I spent a very interesting morning at the University Orthopaedic Hospital which is under Professor Dittmar. This Hospital is about six miles out of Heidelburg, and is beautifully situated on the bank of the River Nekar. It is delightfully appointed with up to date equipment. An interesting room was the physio-therapy department. After the war, the hospital was filled with war disabilities of an orthopaedic nature, and in order to economise in masseuse, a great variety of most ingenious apparatus was devised and made very largely from parts of guns.

I saw Professor Dittmar explore the knee joint for a suspected cartilage displacement. This incision was a long one medial to the patella, which was turned outwards to give a wide exposure of the interior of the joint. He used no tourniquet, but was especially careful in his haemostasis passing a needle with ligature around each clipped artery. The cartilages appeared normal but a calcified nodule in a fatty fringe was found and removed. Professor Dittmar was not an advocate of spinal anaesthesia. Ether was used.

The second operation was for a persisting congenital dislocation of the hip in a child of about six years old.

The upper margin of the acetabulum and the head of the femur were exposed through a vertical incision just behind and above the great trochanter. There was no hour glass contraction of the joint capsule so the head was easily manipulated into the acetabulum. An osteotome was then driven into the ilium just above the acetabular margin, and a portion of the tibia then driven into the hole made by the osteotome. The end of the tibial piece projected over the replaced head of the femur by about half an inch or more. The wound was closed and previous to plastering was inspected by X-ray and a special viewing box (a great convenience). After plastering, it was again viewed.

Congenital dislocation of the hip is an extremely common condition in the neighbourhood of Heidelburg. There were five or six in the hospital when I was there. Manipulative treatment and plaster according to orthodox scheme is favoured in the early years, but the feeling is that the majority come finally to open operation.

An interesting point about this hospital is that a departure is made from the traditional uniform colouring of all the wards and corridors. Each floor has its attractively different colour schemes.

At Edinburgh, I spent three months. In contradistinction to Heidelburg and the London Medical Schools (barring the new Post

Graduate School at Hammersmith), the post graduate arrangements are excellent and attract people from every part of the world. Access is given, (albeit only as spectators) to every department of surgery and medicine and the care and enthusiasm with which lectures and demonstrations are presented deserves the highest praise.

There, one was able to get the trends of thought which was impossible in Germany owing to the language difficulty.

Firstly, with regard to fractures. In the realms of theoretical and speculative there rages the battle of the osteo blasts in which there are two camps; those who hold that there is a specific cell endowed with ability to form bone, and those who following the French surgeons Le Riche and Policard, hold that bone formation is a tissue response to certain conditions of chemical environment and ischaemia. From which emerges an Edinburgh shibboleth. "Hyperaemia means osteosclerosis." Greig, the curator of the museum of the Royal College of Surgeons has written a very interesting book on the subject.

Some very interesting work on the healing of fractures is being done by Stirling. He is investigating the changes in the callus during the early days after the fracture, and has found that during the first fourteen days, the reaction of the haematoma (which is virtually encapsulated) is acid—this is the period of the mobilization of calcium from the fracture ends of the bone and elsewhere. It then swings over to the alkaline side of neutrality with the beginning of the deposition of calcium. New haemorrhages delay this change. He is now experimenting with the injection of a calcium solution of the correct p.H., and early results are encouraging, though with a laudable Scottish caution, he will not as yet pronounce any verdict.

Plates of metal are liable to interfere with the correct reactions, and are, apart from this consideration, regarded with distaste. It is held that trouble very frequently results sooner or later.

The principles of Bohler of Vienna are accepted as a sound working basis and Kirschner's system of extension is used—the working rule being that the fractured ends of the bone should be moved as little as possible (ideally not at all) and the muscles as much as possible.

The autonomic nervous system is very much in the lime light. Various parts of it are being removed for such widely remote conditions as angina pectoris and Hunner's ulcer of the bladder. This branch of surgery seems to be still in the experimental stage, and it seems likely that the most important results will be an elucidation of the very largely unknown influences played by the balance of two antagonistic nervous controls on the viscera. One rather interesting fact has recently been discovered: the removal of the pre-sacral nerves in the male is followed by the inability to consumate the sexual act by an orgasm—a very important defect, especially psychologically.

The immediately good results in Raynaud's disease are not held to be entirely permanent.

Professor John Fraser is a strong advocate of the removal of the stellate ganglion for angina pectoris. He removes it through an anterior incision which makes the operation, as he remarks, an excellent excercise in the anatomy of the root of the neck.

With regard to radium, I was unfortunately not able to visit Beechmont where most of the radio therapy is carried out. But I think this is a fairly accurate summary of the current ideas.

Extirpation surgery is the rule as the first line of attack if the growth is accessible, and radium is held to be a valuable adjuvant; except in cases of carcinoma of the anterior third and middle third of the tongue, intrinsic carcinoma of the larynx, and carcinoma of the cervix. For rodent ulcers, some excise and others use radium primarily, depending to some extent on the degree of advance of the growth.

Radium is used in plaques, in needles, and recently, one gramme has been put aside for a radium bomb. This is used for, among other things, growths of the posterior third of the tongue the fauces and tonsils, the pharynx and larynx, and supplemented by dental and other small surface applicators for tumours of the upper and lower jaws and the maxillary air sinuses.

The system of dosage is very carefully worked out by a specialist in close measurement to get a uniformity of irradiation. The technique of this is beyond me, except that Seivert's condenser chambers are used and the calculation done from Stahel's iso-dose curves. The feeling is very strong that radium is a form of therapy that should be confined to a specialist; and the dosage should be estimated by some one trained in the physics of radium.

In view of the difficulty of diagnosis of carcinoma of the tongue from the occasional tuberculous ulceration and syphilis, diagnostic section is never made until radium is available for immediate insertion after the section. A period without radium after the section is strongly contra-indicated. If section shows a growth and the condition of the patient and glands warrant it, a block dissection of the lymph nodes of the neck is performed. Should the section prove the ulcer not to be malignant, the radium is immediately removed, and it is held, that for leukoplakia, the effect is at least beneficial.

Carcinoma of the breast is treated by radial removal followed by prophylactic deep X-ray irradiation, provided it is still in the operable stages. By this means they claim the following results, grouping breast cancer in three groups :—

I. Cases in which growth is confined to the breast tissue, with no lymph node involvement. (i.e., no fixture).

III. Cases in which growth is not fixed with lymph node involvement.

III. Cases where the growth is not confined to the breast and there is wide lymph node involvement.

Group I cancer is considered one of the most curable forms of cancer if a radial operation is performed. Their follow up figures show a 100% 2 year cure rate and an 80% 5 year cure rate.

Group II shows a 70% 2 year cure rate and 20% 5 year cure rate.

Group III. All were dead in three years and 70% in one year.

Radium was used for the inoperable group III cases, but it is admitted that inadequate dosage has been used; nor has any standard scheme of treatment been instituted.

A combination of radium followed by surgery is sometimes used.

There is much argument about the relative merits of medical treatment, excision and short circuiting for ulcers of the pyloric and duodenal regions; but I think it is agreed among all, that a thorough medical course should be tried first except in old stenosing ulcers, and I may say that I saw no partial gastrectomies done in the course of my stay in Edinburgh in contra-distinction to Germany.

The dicta of Sir David Wilkie on this subject are very interesting. According to his experience, the results of gastro-jejunostomy in cases with a high hydrochloric acid curve are bad. In fact, he says, it is asking for trouble in the form of an ulcer near the stoma. For gastro-duodenostomy he claims moderate results. Should a stoma ulcer follow, he suggests subsequently doing a gastro jejunostomy.

For old cicatrized ulcers, he advocates a gastro-jejunostomy, and apparently in these cases the HCl. curve is usually normal or low.

For old ulcers on the lesser curvature, he advocates ablation or partial gastrectomy, and finally, for old patients with a penetrating ulcer high up on the lesser curvature, he advocates a gastro jejunostomy.

To consider some small points of technique, anastomosis clamps are not used. Wilkie has a very neat and simple little instrument in the form of an oblong of thin metal rod, with a knob at each end. He approximates the two bowels with stitches at each end of the proposed region to be incised, ties the stitches and then puts the region on the stretch by winding the suture ends round the knobs.

Fraser makes a great point about ligaturing the individual blood vessels before starting any sewing and puts a double sero-serous layer anteriorly. Before starting to sew, he swabs the whole region with tincture of iodine.

Mr. Harry Wade is particularly interested in kidney conditions. In the course of kidney investigations he does both excretion urography and pyelograms by injecting opaque material into the pelvis. The former gives physiological indications and the latter anatomical.

He has done lately with great success, transplantations of the remaining ureter in cases of excessive bladder irritability and contraction following tuberculosis of the kidney and bladder, in which the disease is unilateral and one kidney has been removed.

He does not introduce ureteric catheters at the time of operation, as does Coffey, but passes a strand of catgut up the ureter, one end of which is passed through with a needle the cut end of the ureter and used for drawing the ureter into the lumen of the bowel and passed through the bowel wall to anchor it. One end acts as a wick in the ureter. The other end anchors the ureter. The wick is sufficient to overcome swelling and occlusion by the end of the ureter. The rectum is drained with a catheter to show if the kidney is excreting. Should there be any signs of suppression, he gives a 4% sodium sulphate solution intravenously and continuously by the drip feed method.

If the operation is successful, these people from being wretched, useless individuals, can go for periods of four hours and more without passing water.

Interesting work has been done on the so called B.C.C. pyelitis which is held on the strength of very excellent whole organ sections, (beautifully executed by Mr. David Band), to be really a pyelonephritis. A paper on the subject by him is printed in the Edinburgh Medical Journal No. 5, 1933.

He holds that part of the trouble is atony of the pelvis and ureter with stagnation, following an original mild infection. From the stagnation, there is a back spread into kidney substance. In the event of failure of diuretic treatment or ketogenic treatment, he claims good results from ureteric catheterization, washing out the pelvis with weak silver nitrate solution, and drainage for 2 days with the indwelling catheter. Very good results are claimed for the ketogenic diet treatment provided there is a pure B.C.C. infection.

I paid a very interesting visit to the orthopaedic hospital at Fairmile-head where we were shown round by Mr. Cochrane. The hospital is beautifully situated well in the country outside Edinburgh. It is built on the pavilion system with wide unroofed verandahs. Here it is attempted to collect all orthopaedic cases from the Eastern counties of Scotland.

Excellent orthopaedic work on polio-myelitis is being done here; and it would seem that much longer periods of rest to the paralysed muscles should be given than is usually advocated. In the earlier stages until the complete absence of tenderness, treatment should consist of rest, absence of irradiation and avoidance of meddlesome therapeutics. Later specialized muscle training treatment is given to re-educate the muscles, to their diminished nerve supply.

To quote Cochrane: "Muscle training is fundamentally an attempt to restore a cerebral motor impulse to a muscle. It aims at forcing the efferent impulse to develop a new path and to secure contraction of the desired muscle however feeble. A permanent improvement in conductivity is thus obtained and the muscle is given a small dose of excercise appropriate to its enfeebled capabilities.

The patient's whole attention must be concentrated on the attempt, which is carried through the whole arc of the joint movements by the assistance of a trained masseuse, who supports the limb and eliminates the effects of gravity; the resistance at every point should be a little less than would stop the movement.

The exercises should not be done alone but require the assistance and outside stimulus of a trained masseuse."

Muscle training is considered to be the best *single adjunct* in the hands of an expert.

The chief points seem to be:—long periods of relaxation of affected muscle before starting treatment—long periods of rest before anything like hard work for the muscles. For instance, a year is suggested before walking is attempted is paralysed leg muscles, and expert muscle training with psychological encouragement as opposed to massage and electrical stimulation. Osteomyelitis is treated on the Winnett-Orr principles with alleged success.

I cannot leave the subject of Edinburgh without comment on the excellence of the Museum of the Royal College of Surgeons which is under the Curatorship of Mr. Greig. Specimens are beautifully preserved and presented and carefully described. If there is one criticism, it is that there is not a single normal specimen in the whole museum. A normal at the end of each series for comparison would be of great value.

I was only able to spend a fortnight in London as an onlooker at Guy's Hospital. Here, as in Germany, very little provision is made for the post-graduate. As the aim is to provide the actual students with an abundance of practical opportunity without much lecturing, the majority of the teaching is carried out at the bedside and in the operating theatres, and in each case, the students are an intergral part of the working system of the hospital. While this system may not turn out the learned physician or surgeon, it is calculated to produce a man of practical ability.

A feature at Guy's Hospital is the "Combined round". On two afternoons a week, rounds are made in the medical wards, (why not in the surgical wards, I do not know), which are attended by three or four visiting physicians and not infrequently surgeons. Cases are seen and demonstrated by the ward clerks or house physicians and physicians in charge of the cases, and are discussed by everyone interested. Not infrequently there will be present a physician, a surgeon, a pathologist and a psychologist. This is of great value to those beyond the stage when the fundamentals are still being painfully sorted out and dogmatic pronouncements necessary for a foundation. To these, it is probably confusing to hear conflicting views, but it must nevertheless, stimulate development of an early discriminating ability. Also, one sees in it the beginnings of the time when diagnosis and treatment will be much more the outcome of a closer co-operation of a group of specialists than it is now, when the pathologist's opinion is often a few words on a piece of paper, the radiologist's another syllable or two on another piece of paper, and the oto-rhino-laryngologist has not listened through a stethoscope for an age.

A new anaesthetic, cyclo-propane is being tried out in London. This is a heavy gas which is extremely economical to use, as a small quantity introduced to a closed circulation is exhaled and rebreathed over and over again, adjustments of oxygen being made as necessary and carbon dioxide absorption arranged for in the system. Anaesthesia takes place quickly and comfortable and reasonable relaxation results. The gas is, however, extremely explosive and will sink to the lowest part of the building, possibly the kitchen with disintergrating results.

Ogilvie has a very interesting arrangement for keeping his table tidy in the course of an operation. He has a rack which is placed on a slant towards the middle of the operating table, and within reach of the surgical dresser and instrument sister. Each type of instrument has its appointed place and is replaced when out of action, so that there should never be any fumbling about in search of illusive scissors or dissecting forceps.

I saw Peterson's pin used on two occasions for fractured neck of the femur, but it is still considered to be "subjudice"; Kirschner's method of extension is much in use and considered a valuable measure.

Speaking generally, there seems to be very little difference in the views held in London and Edinburgh, except that in Edinburgh when in doubt, they murmur "Tuberculosis", in London, they mutter "Syphilis".

A course in Dental Surgery is now essential for the London degree so there are courses in the dental school for medical students.

I spent a very interesting afternoon in the children's dental department and was much impressed with the care which is taken in preserving as long as possible by fillings, etc., the first dentition. The correct occlusion and disposition of the second dentition, it is said, is very largely dependent on preserving as long as possible the milk teeth, and septic carious dental conditions must have an effect on the lymph ring round the pharynx. The child should have as frequent if not more frequent dental inspection as the adult.

In conclusion I feel that this paper must appear to be like an amateur's album of holiday snapshots, some badly developed others badly focussed, but I hope that here and there one will stand out interestingly.

TOXAEMIA OF PREGNANCY*

by

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One has been impressed by the high incidence of toxaemia of pregnancy amongst the women attending the obstetric clinics which one supervises. Whether this condition is met with so frequently amongst the private patients whom you attend it is impossible for me to say. At all events those of us who practise obstetrics will at some time or other be face to face with this complication of pregnancy. Another reason for my choice of this subject as a post-graduate lecture is that this condition is second to puerperal sepsis as the cause of the greatest number of maternal deaths.

You will require some confirmation of my previous statement as to the high incidence of pregnancy toxaemia in this part of the world, and it is therefore necessary to review statistics on this point. In England the incidence is approximately 3%, in New Zealand 5% (1) and in Hong Kong 7%. Last year in the University Obstetric Clinics of the Government Civil and Tsan Yuk Hospitals there were 2,351 deliveries and of these 159 had toxaemia of varying degrees of severity. There were 9 cases of eclampsia with 2 deaths. Baird (2) of the Glasgow Maternity Hospital has recently revealed a most disappointing fact, namely, that there are just as many cases of toxaemia now as there were twenty years ago. On the other hand, the incidence and consequently the death rate from eclampsia is definitely lower in those patients who have had ante-natal care than in those who have had no supervision during pregnancy.

I regret I cannot avoid giving you some statistics. Doubtless you will know that there are three kinds of lies—white, black and statistics! I put these figures before you since they serve to emphasise the gravity of the disease. Eclampsia has a maternal mortality of 25% and a foetal death rate of 50%. It is not only the immediate risk but the remote complications and chronic ill-health which follow toxaemia which must be realised. Gibberd, (3) of London, has published some most illuminating figures. He followed up after delivery a series of toxaemic cases and divided them into two groups. Group A were patients who had had their toxaemia for three weeks or less before they were delivered whereas Group B had been toxaemic for three weeks or more. In Group A 5% developed chronic nephritis and recurrent toxaemia was found in 36% who became pregnant again. In Group B, 28% showed definite nephritis and the recurrent toxaemia rate was 76%.

* Post-graduate lecture given at Hong Kong University on April 20th, 1936.

The significance of these figures is obvious. The longer a patient remains toxaemic the more risk is there of chronic nephritis. The seriousness of this needs to be emphasised since 40% of chronic nephritic women are dead within 10 years. Again, it is no help to the baby for it to be allowed to continue in utero under the continuous effect of the toxaemia. These babies are usually premature and, if they survive their birth they remain below normal for many years. They are much more prone to infections in childhood than those babies born of non-toxaemic mothers. We have all made mistakes in the past of allowing a patient to go on week after week with her toxaemia, coaxing her on to the thirty-sixth week, if possible, in the hope of getting a larger and stronger baby. One should not consider the baby in these cases, it is the mother's life, present and future, which we must safeguard. Again there was a false dictum that "once an eclamptic never again an eclamptic in a subsequent pregnancy." Let us correct that and say: "once an eclamptic 15% chronic nephritis, 7.5% recurrent eclampsia, 20% recurrent toxaemia, a greater risk of pulmonary tuberculosis."

The death rate from toxaemia is less now than it was ten years ago and this is due to better ante-natal care and earlier termination of pregnancy. One point to be stressed in ante-natal work is the routine which should always be adopted of taking the blood pressure. The diastolic reading is just as important, even more so, as the systolic. There may be a rise of blood pressure in pregnancy toxaemia a fortnight before albumen appears in the urine or any other symptom or sign develops. The importance of this finding is that treatment can be started when the toxaemia is in its early stages. In passing I should like to mention some observations that Professor Ride of the Physiological Department has just made. He has found that there is a group of normal adult Chinese in whom blood-pressure readings are consistently low. A normal average reading in these individuals is 96/70. As the result of these observations we shall have to readjust our views as to what is high blood-pressure in toxaemia. We might be dealing with a patient belonging to this group. Seeing her for the first time in a pregnancy toxaemia, a blood pressure reading in her case would have to be considered high which in another woman would pass as normal.

The cause of toxaemia is unknown. Every conceivable suggestion has been put forward—constipation, increased intra-abdominal pressure, deficiency of calcium, vitamin lack, absorption of abnormal protein products from the placenta, and so on. We are living in an endocrine era and endocrinologists have not been slow in considering toxaemia as due to hormone imbalance. From the posterior pituitary a vaso-pressor substance is excreted in excessive amounts. It has an anti-diuretic action causing water retention and also it effects by spasm the terminal vessels. In this way the pathological changes associated with eclampsia are explained.

Prognosis in Eclampsia.

One knows too well that the first question the anxious relatives will ask the doctor after he has seen the patient will be, "is her condition serious"? It is possible to divide cases into two groups, the mild and the severe. A serious case and therefore one of bad prognosis is that in which (1) the temperature is over 103° (2) the pulse is more than 120 (3) the blood pressure is higher than 170/100 (4) the number of fits are over six (5) the fits occur in rapid succession (6) there is coma (7) there is anuria (8) there is little albumen in the urine (9) oedema is slight (10) pulmonary oedema is present (11) the heart is failing. These observations merely serve as a guide in prognosis and it must not be inferred that because a patient exhibits these signs that she must surely die.

Treatment.

Treatment is what must obviously interest you rather than hypotheses which change from day to day. On making the diagnosis of toxaemia treatment must be started without delay. In the mild cases one puts the patient to bed, directs attention to her bowels (magnesium sulphate is the best purgative in these cases), restricts the diet, gives diuretics, glucose and iron. The value of glucose is indisputable. It is an excellent diuretic, it reduces oedema (especially cerebral) by its osmotic action, it protects in particular the liver. For it to be effective the concentration must be high—℥vi of glucose to 1 pint of orange or lemonade. If under strict medical treatment the patient's condition becomes worse, or new signs and symptoms develop, pregnancy must be terminated at once by rupture of the membranes.

Technique of artificial rupture of the membranes.

No anaesthetic is required and only one instrument, namely, a pair of Kocher's forceps. With proper asepsis and antisepsis the index finger of the left hand is passed into the vagina up to the cervix, the forceps in the right hand are guided along this finger into the cervical os. An assistant exerts supra-pubic pressure on the presenting part in order to tense the fore-waters. The membranes are nipped with the forceps and the liquor gushes out. The whole of the uterus is firmly palpated in order to express all the liquor. This is the surest, safest and easiest method of induction of labour.

The treatment of eclampsia is complex and diverse. There are different schools of treatment—Stroganoff, Dublin, London, surgical—and each has a few or many points in its favour. Perhaps the best is the "composite" school in which some item of treatment is stolen from each of the others. There is not time to discuss fully the treatment of eclampsia but I would like to stress the importance of intravenous glucose in high concentrations—50 c.c. of 50% solution repeated within four hours. Coramine, 1 c.c., should be given four hourly and if the patient is not in labour the membranes should be ruptured. These are only a few of the points in treatment.

Conclusions.

(1) Toxaemia of pregnancy is more common in Hong Kong than in Europe or New Zealand.

(2) The public must be educated to the realization of the importance of ante-natal care.

(3) Ante-natal examination must be thorough, neither hurried nor careless. It is an idle boast of a doctor in charge of an ante-natal clinic to say that he or she sees sixty ante-natal cases in a morning session. Such practice is to be deprecated.

(4) A raised blood-pressure (particularly diastolic) is one of the most important of pre-eclamptic signs. Therefore taking the blood-pressure must always form part of one's routine in the examination of a pregnant woman.

(5) There must be no hesitation in inducing premature labour if there is no improvement in the patient's condition whilst under strict medical treatment. Artificial rupture of the membranes by the method already described is to be strongly recommended.

(6) Finally, death from eclampsia can be avoided in most cases by intensive ante-natal care.

The following is a brief summary of the discussion which followed the above paper:—

Dr. Samy stated that in his experience the hospital incidence of eclampsia was about 7% and in general practice about 2%. There was a decided seasonal variation, the condition appearing to be more common in the spring than at any other time. He asked if Professor Nixon's figure of 25% mortality came from hospital records or from the general population. He was convinced that the treatment of the Dublin school was the best especially if followed right through.

Dr. Hilda Yuen observed how difficult it would be to tell the actual duration of the toxaemia of the "B" group of three weeks' standing or more. She enquired as to how one could be certain when the toxaemia had started.

Dr. Teh asked how long after delivery was it usually considered that fits were post-partum eclampsia in origin. He discussed a case in which the typical fits occurred 28 days after delivery.

Dr. Laing considered that induction of labour by rupturing the membranes might fail sometimes. He wished to know the length of time after rupture of the membranes before labour started and also how long one should wait before trying other methods.

Dr. Ozorio was of the opinion that Professor Nixon's explanation of the method of rupturing the membrances sounded easy but that in actual practice it could be difficult, particularly, in a primipara in whom the cervical os was closed.

Dr. Karanjia asked at what rate was glucose administered intravenously.

Professor Ride suggested that there might be difficulties in applying the glucose treatment in a case of eclampsia complicated by diabetes. If tha glucose in these cases acted merely as a detoxicating agent in the liver, would the giving of insulin help?

In reply Professor Nixon said that the figure of 25% was taken from the report of the London Committee appointed by the Royal Society of Medicine and the cases investigated were those of all clinics who published their results. Gibberd's analysis was of patients attending his ante-natal clinic and the toxaemia was noted from its onset whilst the cases were under observation. It was difficult to say how long after delivery that fits could be called eclamptic but the speaker thought that 28 days seemed to be rather a long time. After rupture of the membranes labour usually started within twelve hours. Even in cases where the cevical os was closed it was possible to introduce a small pair of Kocher's forceps. Regarding intra-venous glucose, for a small amount such as 50 c.c. one should take five minutes for the injection but for larger amounts where several litres are given it was best to use the continuous drip method and to take several hours over the administration. Professor Ride had supplied the conundrum of the evening. Fortunately to meet diabetes and eclampsia in one and the same patient was rare. Provided one gave insulin there was probably no harm in giving the glucose treatment even though the eclamptic might be a diabetic.

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THE CYTOLOGICAL BASIS OF THE CHROMOSOMAL THEORY OF HEREDITY

by

Lindsay Ride.

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Science has not yet been able to penetrate the abysmal deep that separates things animate from things inanimate but it has already carried light far into that gap of ignorance which separates living bodies of succeeding generations; the method of genesis of that mysterious filament we call life still lies beyond the borders of our understanding, but the means by which this line of life is handed on for temporary keeping from individuals to individuals, already falls within the limits of our meagre scientific knowledge. Life is one of the most remarkable of the many characteristics of that special substance which we call *protoplasm* and in the higher animals and plants this protoplasm is contained in more or less defined units known as *cells*, while in the lowest forms of life one such cell may compose one entire individual. Multi-cellular animals we know are derived from one single fertilized egg by a process of repeated cell division and sub-division, and hence it is not surprising to find that biologists look on the cell as the unit of things living, and that if we wish to understand the way in which characters, and even life itself, may be handed from cell to cells or from individuals to individual, we must first understand the structure of the cell and its method of sub-division.

The Cell.

Cells vary greatly in size, shape and functions but they all more or less conform to a certain fundamental structural plan. In general a cell is composed of a mass of protoplasm, limited and enveloped by the cell membrane whose semi-permeable character allows ions, atoms, and molecules—both gaseous and liquid—to pass, according to the dictates of physical laws, between the imprisoned protoplasm and the environment of the cell, retaining within the cell the protoplasm itself and the other important cellular structures such as nucleus, centrosome, plastids, mitochondria and Golgi apparatus. Of these the most constant and most important from our point of view are the centrosome and the nucleus and to these we shall confine our attention. The protoplasm of the nucleus is separated from that of the rest of the cell by the ***nuclear membrane*** and as the nuclear protoplasm is distinct from that of the rest of the cell, the former is termed ***nucleoplasm*** or ***karyoplasm*** to distinguish it from the latter which is known as ***cytoplasm***. The nucleoplasm is not homogeneous but contains a network of denser staining material known as ***chromatin***, and one or more still denser masses, the ***nucleoli***. The chromatin material is considered to be composed of small granular masses mounted on threads of *linin*, a fact of some importance to the modern theory of genetics as we shall explain later. The centrosome, although not always present in plants, is found fairly constantly in animal cells and is a small bi-lobed body frequently surrounded by rays of cytoplasm referred to as the *aster*. This body along with the nucleus, plays a definite and important part in cell division. The other cytoplasmic entities mentioned, plastids, vacuoles, mitochondria, etc., are not constant in occurrence nor do they seem to take any active part in cell division, so they need no further elaboration here, our aim being to discuss only those parts of the cell which play a part in modern theories of heredity. (Figure 1).

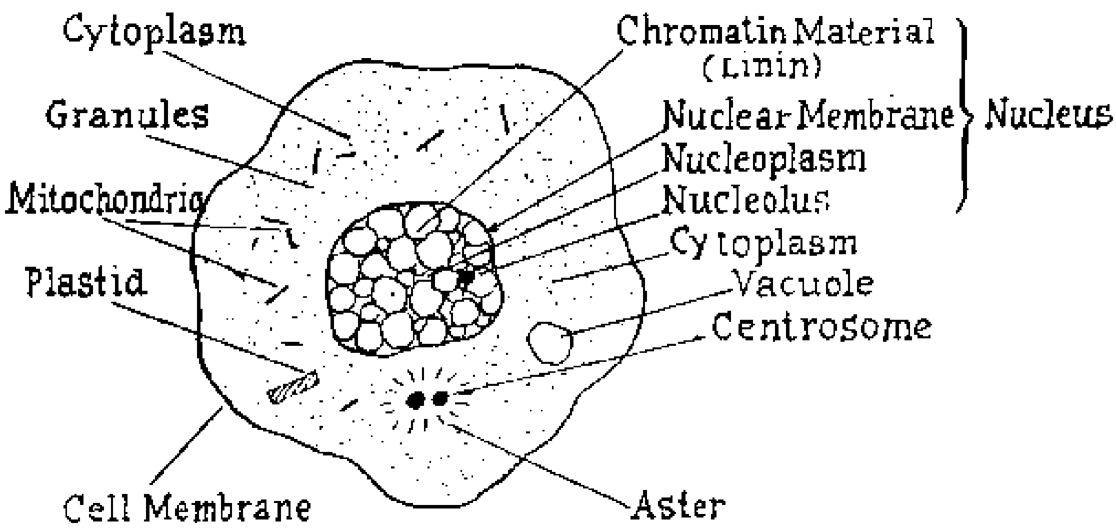


Figure 1. Diagram showing essential constituents of a typical cell.

This brief discription of the cell is true in general, but body cells may be distinguished from one another by variations in details of size and shape, proportion of nucleoplasm to cytoplasm, presence of granules and plastids, etc., and thereby is the histologist enabled to differentiate muscle, bone, gland, epithelial, blood and many other types of body cells. In one condition however this whole plan becomes fundamentally changed and that is when the cell is undergoing the changes that accompany cell division, the process whereby bodily growth is made possible in multicellular animals, and whereby new individuals are formed in unicellular organisms. In this change the nucleus first divides into two, followed by cytoplasmic division, so that the parent cell gives rise to two similar daughter cells. The change which the nucleus undergoes during this type of division is known as *mitosis* or *karyokinesis*, a term which is often applied as well to the division of the cell as a whole.

Mitosis.

Besides its well known physiological functions, the nucleus plays a leading part in cell division; just as the nucleus can, by centrifugalisation, be shown to be denser than the surrounding cytoplasm, so one or two portions of the nucleus, the nucleoli, can be shown to be denser than the rest of the nucleoplasm. However, as the cell prepares to divide, the nucleoli break up and are not again separately distinguishable until the resting stage following completion of cell division. It is owing to this temporary disappearance of the nucleoli that they are not considered to play any important part in the mechanism of inheritance. With the other distinguishable part of the nucleus, the chromatin, it is different. In the first phase of mitosis, the *prophase* (Figure 2a), the chromatin may be seen in coiled double threads which later will be recognised as *chromosomes*. It should be noticed that even at this stage each chromosome is composed of two exactly similar double threads lying parallel to one another, each constituting a *chromatid*. Gradually the chromosomes assume shapes and sizes which are constant and characteristic of each, and when they are thus formed, it is seen that they exist in pairs, each pair being composed of two apparently identical chromosomes. But whereas the chromatid pairs remain closely associated in the chromosome, each homologous chromosome seems to exist in the nucleus independently of the other. At this stage of the cell cycle the nuclear threads are seen to present a beaded appearance due to unequal stain affinities of different parts of the chromatin material; the appearance of the chromosomes at this stage is that of darkly staining beads, *chromomeres*, mounted on lighter staining chromatin threads. The linear order of the chromomeres in any one chromosome is constant and serves as cytological evidence for the assuption of the constant linear order of genes already discussed (3).

As the prophase progresses the chromosomes become shorter and thicker owing most probably to some water exchange between the chromatin and the nuclear sap, and the end of the prophase is marked by the attainment of the maximum decrease in length of the chromosomes, and thus whereas during the resting stage the chromatin is so dispersed in its fine net work throughout the nucleoplasm that it is hardly detectable, at the end of the prophase it is mobilised into the discrete pairs of chromatids which are stainable and recognisable with relative ease. All trace of a real nuclear membrane has by this time definitely disappeared and the changes above described in the nucleus seem to take place freely in the cytoplasm of the cell. This makes possible the important association of the centrosome and the nuclear material. The centrosome is usually a double body and during the prophase it develops striations in the surrounding cytoplasm forming the *centrosphere;* the two parts of the centrosome then separate, and pass to opposite sides of the nucleus. The striations connecting the two centrosomes give the appearance of fibres stretching through spidle shaped protoplasm and these fibres are therefore known as *spindle fibres*. The characters of the dividing cell at the end of the prophase are thus the mobilization of nuclear chromatin into chromosomes or paired chromatids and the separation of the two parts of the centrosome, one to either side of the nucleus, each being connected to the other by spindle fibres. (Figure 2b).

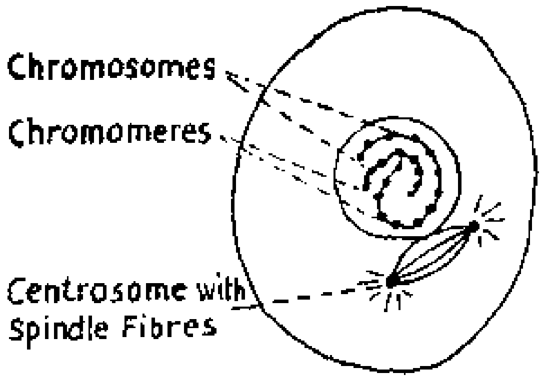


FIG. 2a. Early Prophase showing centrosomes moving towards opposite sides of the nucleus and chromomere formation of chromosomes.

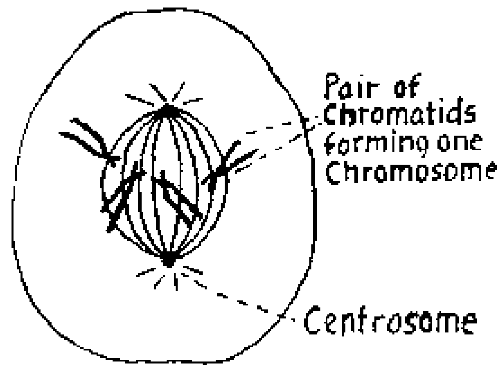
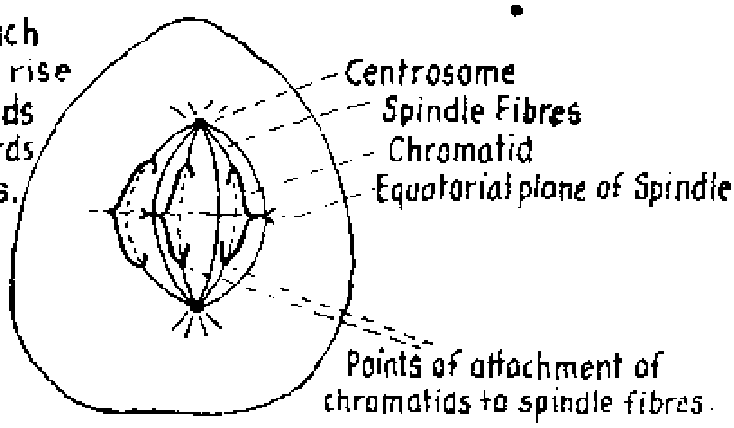


FIG. 2b. Late Prophase showing absence of nuclear membrane, attachment of chromatid pairs at equatorial plane of spindle fibres, and disappearance of chromomeres owing to contraction of chromosomes.

FIG. 2c. Anaphase. Each chromosome is giving rise to two separate chromatids each being drawn towards one of the centrosomes.



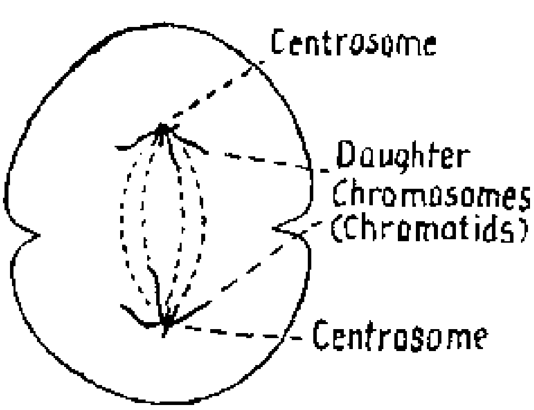


FIG. 2d. Telophase. The chromatid pairs have now completely separated giving rise to daughter chromosomes congregated around the centrosomes.

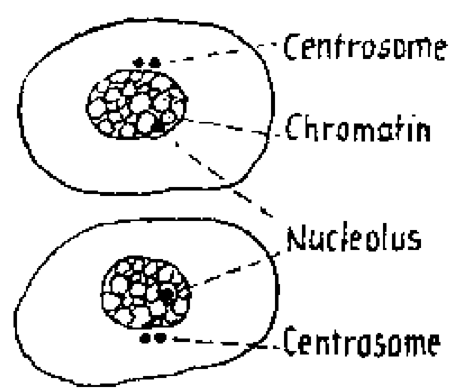


FIG. 2e. Two new daughter cells, their nuclei formed from the chromatin material attracted to each chromosome.

The next stage is known as the *metaphase*, and is characterised by the fact that now the chromatid pairs assemble in the equatorial plane midway between the centrosomes and appear to be attached to the spindle fibres at a definite point of attachment which varies in its position in each chromosome. All sign of the chromomeres has by now disappeared owing to the contraction of the chromosomes, but each chromosome may exhibit one or more lightly staining gaps which are constant in position and which are termed *constrictions*; the spindle attachment always coincides with one of these, and at this point of attachment the chromatids lie in the axis of the spindle, the rest of the threads lying indiscriminately in the protoplasm. At this point also the chromatids of each pair are most closely united, and as the metaphase progresses, this rigid attachment seems to spread along the chromosome length, and when metaphase is at its height the chromatids are as firmly applied to each other throughout their entire length as they were earlier at their points of attachment. During late metaphase the chromatids begin to move apart, the separation beginning at the point of attachment, the distal ends being the last to separate just as they were the last parts to become firmly applied to one another. It should be noted that at this stage of mitosis there is evidence first of all of attraction forces between the two chromatids of each chromosome, which forces are later overcome as shown by the chromatids separating each to a different pole of the cell.

The next stage is termed the *anaphase* (Figure 2c), and here the separation of the chromatids becomes complete, for they move apart towards the opposite centrosomes as though being pulled there by the contracting spindle fibres to which they are attached. This is a phase which is frequently referred to as that of *chromosome division* but as Darlington (1) points out, this stage is not characterised by chromosome division at all, but merely by the overcoming of the forces which had held the chromatids together ever since they were formed by chromosome division at a much earlier stage in the cell cycle. (c.f., meiosis, p. 100).

The cell now arrives at the *telophase* (Figure 2d) where the separation of the chromatids is complete; they congregate at each pole and there form a compact mass of chromatin material which then undergoes changes which are the reverse of those explained above. By this means each half of the original chromatin material congregated alongside a centrosome, reforms itself into its original state of chromatin network, develops a nuclear membrane around itself, and thus forms another nucleus which is indistinguishable from its partner or its predecessor. An indentation in the peripheral cytoplasm appears between these two newly formed nuclei in the old equatorial plane of the spindle, the indentation deepening until two separate daughter cells each with identical nuclear material are formed. These cells then enter the resting stage which lasts till the next cycle of cell division begins (Figure 2c). The resting stage is characterised by the reappearance of nucleoli etc., and one other very important change in the chromatin material. It is during this period that the chromatin material demonstrates one of its two fundamental characteristics, the power it has to reduplicate its own substance quantitatively and qualitatively, chromosome for chromosome, chromomere for chromomere and, by inference, molecule for molecule. Each particle of chromatin reproduces itself identically qualitatively and then each new particle later grows to its characteristic size. By this means each chromosome comes to be composed of two chromatids, whose separate identity is made apparent by a longitudinal split in the chromosome, but they remain bound together in the one chromosome by some force of attraction which operates as we have seen till the metaphase.

It might be argued that the chromatin is not alone in possessing this power to divide; the cytoplasm exhibits it also; but what is significant here is that when the chromatin divides it must produce new material exactly equal quantitatively and qualitatively to its parent substance, whereas the cytoplasm may—and often does—divide unequally in both these respects (oögenesis q.v.) It is this activity of the chromatin during the resting stage which ensures that the stages of cell division are responsible for the division of the nuclear material into two equal and exactly similar portions, and this equal division of the chromatin material is the essential character of the phenomenon of mitosis.

Meiosis.

We now know that the mitotic plan is not the only one followed by dividing cells. Occasionally certain cells divide so rapidly that the resting stage practically disappears with the consequence that the chromatin material does not get time to double itself as we have seen it does during the resting stage of mitosis. This second method has now been carefully studied microscopically in plants and animals almost innumerable and is known as *meiosis*.

In this type of cell division the beaded chromatin material appears as before in the form of chromosome threads, but the attraction forces are revealed not by cohesion between chromatids—for these are not yet formed,—but by the attraction of each chromosome for another exactly similar to it in size, shape and appearance. This results in the chromosomes being arranged in homologous pairs, and each pair becomes attached to a spindle thread, as each pair of chromatids does in mitosis. It is this intimate association between homologous pairs which gives the opportunity for exchange of blocks of chromatin material between the paired chromosomes, and this is the cytological basis for the phenomenon of crossing over already described, (3) and for the variation in chromosome structure to be described later (p. 104).

The chromosomes now begin to shorten and thicken and then the force of attraction between like chromosomes gives way to a force of repulsion whereby each member of each pair begins to move away from its partner towards the poles of the cells along the lines of the spindle. Thus eventually around each chromosome of the cell is collected one member of each chromosome pair, i.e., half of the original chromatin material. As in mitosis each mass of chromatin material then forms the nucleus of a new cell. It will be seen therefore that each of these cells has only half the chromatin of the parent cell, and a new cell thus formed will be similar to its sister cell on three conditions: (*a*) that the chromosomes present in the parent nucleus are even in number, (*b*) that the division in meiosis is equal, one member of each chromosome pair going to a different centrosome, and (*c*) that each chromosome is exactly similar in chromatin material to its paired homologue. Should any or all of these conditions not hold the daughter cells will differ, and we shall see later how this process of meiosis gives opportunity for the origin of different characters in individuals formed by sexual reproduction (Figure 3).

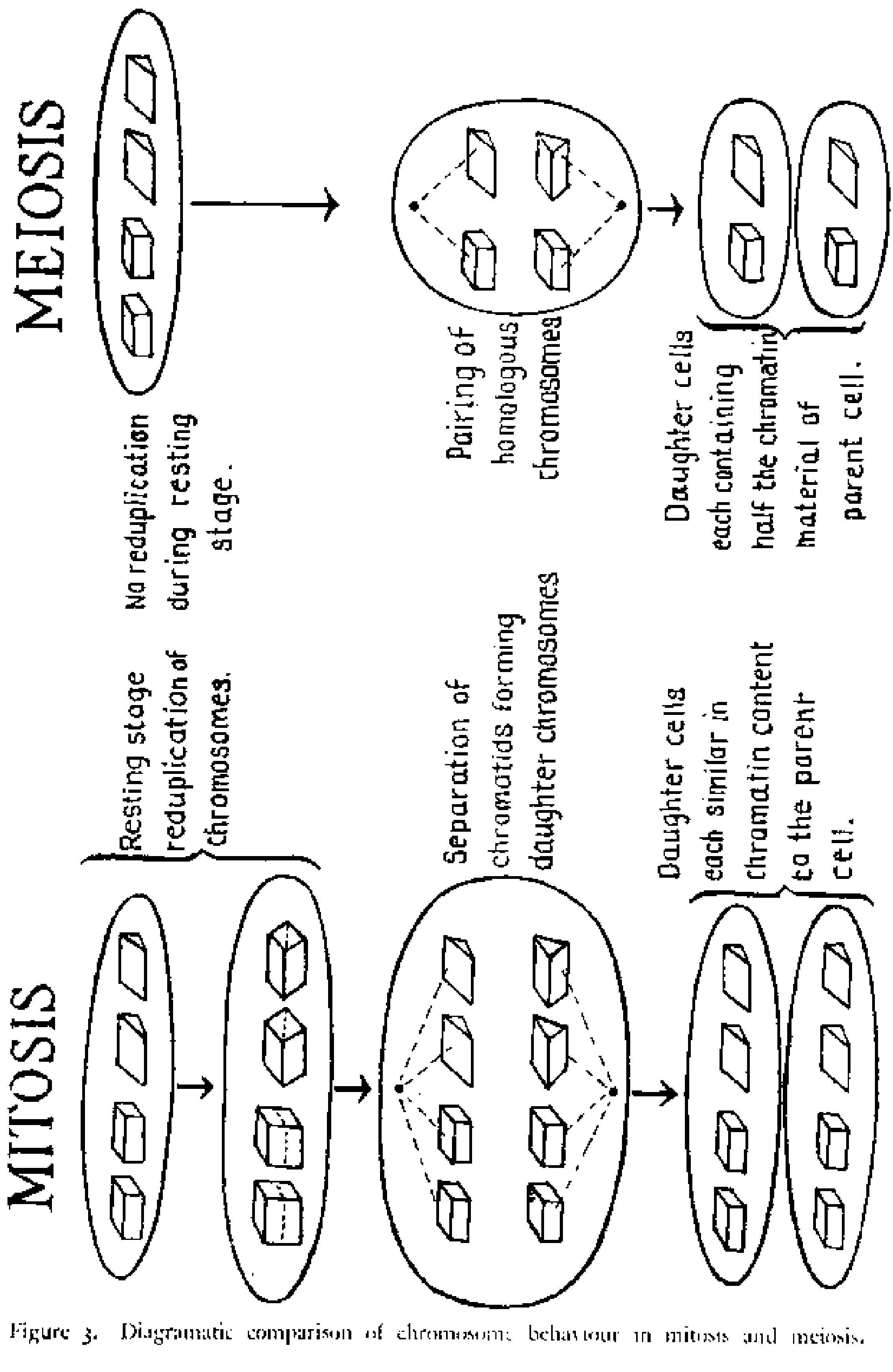


Figure 3. Diagramatic comparison of chromosome behaviour in mitosis and meiosis.

Heredity.

Heredity has been described as that property of organisms or cells in virtue of which they are enabled to reproduce their like.

There are two ideas embodied in the use of the term inheritance, one sociological and the other biological. The former is exemplified in the inheritance by a son of the estates of his father. He inherits such estates ready made from his parent and the condition in which he in turn hands them on to his son depends on how he uses them in his lifetime. The idea of ready made inheritance has had to give place in biology to the idea that a cell does not inherit its characters ready made from its predecessor, but what it does inherit is the ability to develop such characters, and this it inherits in the form of factors supposed to be present on the chromosomes; and as long as cells reproduce by mitosis we can understand how the factors inherited by one generation of cells must be exactly the same as those of the last, and provided the environment be similar the characters developed by these cells in virtue of these factors must also be the same. If this be true, or rather, if this be true of cell division, then all individuals in a colony of unicellular organisms derived from one cell must be identical, and similarly every cell in a multi-cellular animal must be identical with all the others.

Variation.

It is a matter of common observation however that the characters exhibited by cells do vary slightly from those of their parent cell, and that in multi-cellular animals this variation is great enough to enable us to distinguish not only different cells in different organs, but even different types of cells in one and the same organ. Hence any theory of heredity must not only explain how like begets like, but it must also explain the phenomenon of variation as well. We shall attempt to explain the occurrence of such variations under three headings, (*a*) environment (*b*) behaviour of chromatin material, and (*c*) the method of sexual reproduction.

(*a*) *Environment.* Individuals in a colony (or klon as it is called) of unicellular animals such as paramoecia, although all derived from the same individual—and thus having the same genetical equipment—may yet exhibit definite differences in size. This is due to variations in environment caused by differences in food or sunlight distribution, but that the inherited faculties are not altered may be shown by choosing two widely different individuals from the same klon or family and placing them in similar environments. They will be found to produce klons identical with one another, but each showing again similar variations among its individual members.

We find the same thing in multi-cellular animals. Every human being is developed by the repeated mitotic division of cells all ultimately derived from a single cell; thus muscle, bone, brain and gland cells all have the same genetical equipment, but the ectodermal cell develops in a totally different environment from that of the endoderm, and these cells, reacting differently to these different environments, reproduce the differentiation in structure and function which characterises them histologically and physiologically. They still retain however their original genetic equipment and provided their specialization has not progressed too far they may under certain circumstances revert to their earlier undifferentiated characters. This differentiation of cells is shown in the characters of the cytoplasm, while the characters of the nucleoplasm remain unaltered. We may thus look on the cytoplasm as the canvas whereon Nature with but one type of chromosomal brush and many environmental pigments is able to produce those picture variations we describe as cellular or body characters.

Perhaps the best way of illustrating the power that change in environment has of causing different characters to appear in cells having the same genetical equipment is by considering the phenomena of bodily asymmetry and of differences in homologous twins. Apart from the obvious asymmetry of abdominal and thoracic organs, the left side of the body exhibits certain minute differences from the right so that the one is never an exact immage of the other. The writer has recently been able to express these differences quantitativly and qualitatively by investigations into epidermal characters such as fingers prints, palm prints, occipital hair whorls, ear formation and abnormalities. (2, 5, 6). Finger and palm prints are never exactly alike on the two hands of one individual, though they are nearly always similar; the hair over the occiput is generally assymmetrically disposed due to a whorl formation of the emergent hairs; the amount of attachment or freedom of the ear lobe is often different on the two sides and the abnormalities of development such as ear pits are more common on one side than the other. In all these cases the cells of each side have the same genetical factors; they only differ in environment, for the right of the body is in the environment of the left side, and the right side includes the left in its environment. With these exceptions these two environments are very similar, yet the dissimilarity is enough to cause differences in the characters developed.

In the case of homologous twins, again the genetic factors are exactly similar in each individual, but the environments are a little more dissimilar than the examples we have just quoted and hence we would expect such twins to be very similar but not exactly identical in any of their characters. And this is actually what we find, homologous twins are more similar to one another than ordinary siblings but less similar than the two halves of the same individual.

We must remember also that the cytoplasm forms part of the environment of the nucleus, and a change in cytoplasmic characters means a corresponding change in nuclear reaction; we have seen that in cell division there may result inequality of cytoplasm distribution and now we see this itself may result in a change of the characters developed.

and thus may be set up a vicious circle which may well account for differentiation of body cells into the different tissues and organs.

(*b*) *Behaviour of chromatin material.* (*i*) Variation of gene structure. The chromosomal theory of heredity assumes that the factors responsible for the development of inherited characters are carried on the chromosomes and since these latter are paired, the factors are paired also. These factors are most probably of molecular size and structure and it has now been proved beyond reasonable doubt that a slight variation in the molecular structure of a factor may alter its form of expression without altering the character it controls. For example, a pair of factors may control eye colour, causing the appearance of brown pigment: these factors by a slight molecular change may, while still affecting eye colour, be now found to cause the appearance of blue pigment instead of brown. Such a change is called *gene mutation* and we know that in some animals such mutations occur with a definite constant frequency. Should this mutation take place in germ cells it offers an explanation of sudden variations or *sports* found in families of otherwise genetically similar individuals. It should be noticed that the changed genetic equipment caused by such mutation is then passed on to the next generation in the ordinary way, i.e., once a gene mutation which is not lethal occurs, it gives rise to a line of individuals possessing the new factor, and, if this latter be dominant, a new character.

Should this change occur in body cells it is known as a *somatic mutation* and may then be responsible for a morphological or a physiological variation in the body of that individual. It is worthy of note here that somatic mutation is one of the explanations put forward for the origin of cancer cells, and also that mutation can be caused artificially by bombarding chromosomes with emanations from radium or with X-rays. At present this is very much a hit or miss method, but it has already enabled experimentors to produce and establish many different characters in strains of plant and laboratory animals.

(*ii*) Variation of chromosome structure. In general the linear order of chromomeres forming the chromosomes is constant, and from this we infer the constancy of the linear order of genes. It is evident also that the function of a gene depends not only on its structure but also on its proximity to other genes. Hence a variation in chromosome structure even without gene mutation may result in function variation.

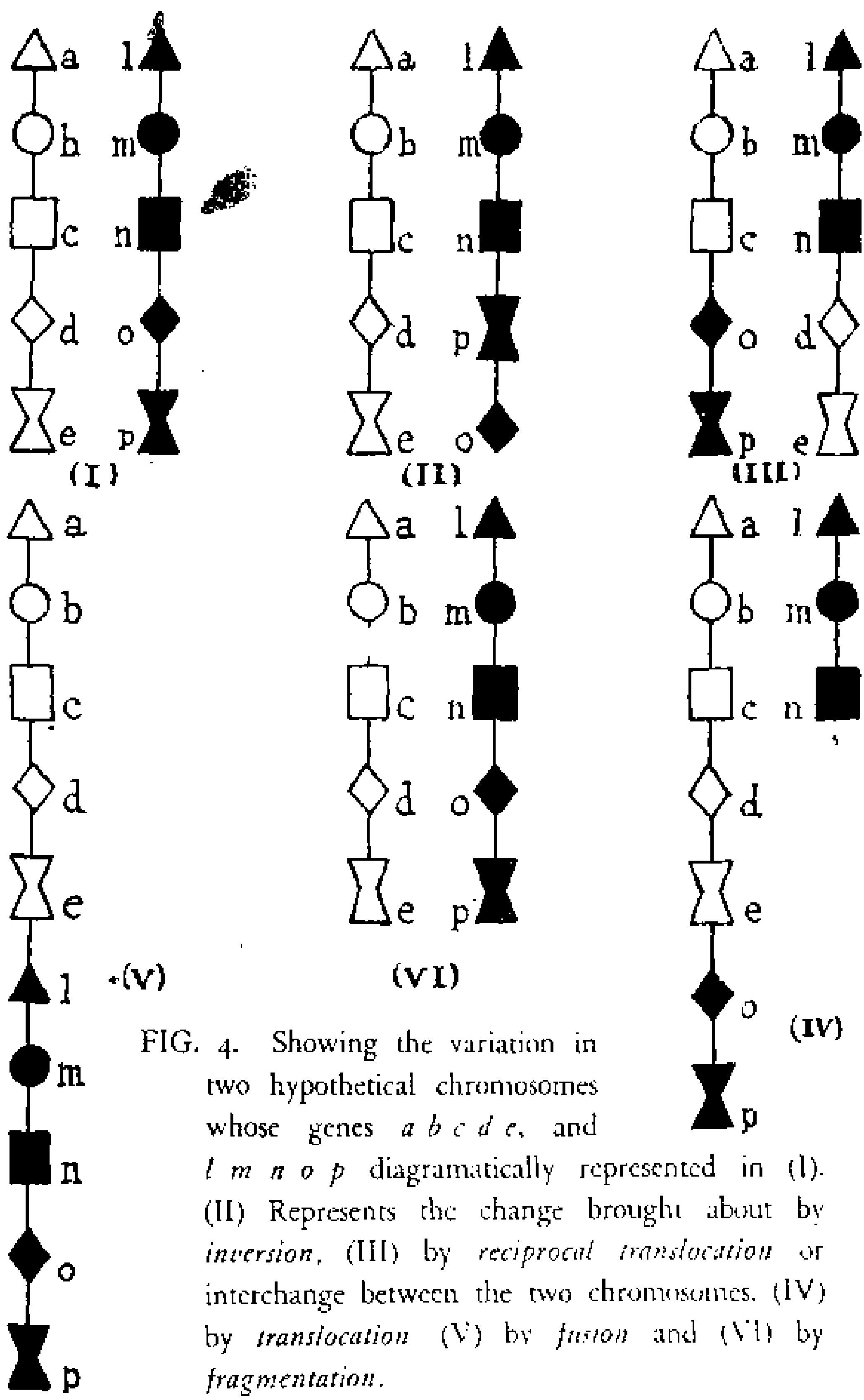


FIG. 4. Showing the variation in two hypothetical chromosomes whose genes *a b c d e*, and *l m n o p* diagramatically represented in (I). (II) Represents the change brought about by *inversion*, (III) by *reciprocal translocation* or interchange between the two chromosomes. (IV) by *translocation* (V) by *fusion* and (VI) by *fragmentation*.

If we denote the linear order of genes by letters we may represent two hypothetical chromosomes as follows, *abcde* and *lmnop*. By the process known as *inversion* we may get interchange of chromomeres giving *abcde lmnpo*: by *reciprocal translocation* or interchange between the two chromosomes, *abcop, lmnde:* by *translocation, abcdeop, lmn,* by *fusion* one chromosome only, *abcdelmnop,* or by *fragmentation* three chromosomes, *ab, cde, lmnop* and so on. (Figure 4). We have already seen how the phenomenon of meiosis gives the opportunity for the chromosomes to behave thus, in fact when we think how the chromosomes have to be called up out of retirement as it were from the resting cell each time it begins to divide, it is a wonder that all these phenomena here described are not found to occur much more frequently than they do. It is this fact that leads us to assume the constancy of the chromosomes in general, subject to the variations here being discussed.

(*iii*) Variation in chromosome number. If all genes be subject to mutations it is only a matter of time when we shall have homologous pairs of chromosomes possessing genes which produce contrasting characters. These genes or factors we have already seen are termed *allelomorphs* (4). When such a state is established the different combinations of these factors will result in different character combinations by means of some further normal and abnormal chromosome reactions; one of the most important of these is the phenomenon of *crossing over*, and how it can be brought about we have already seen.

In our description of the dividing cell we have stressed the constancy in succeeding generations of certain aspects of the chromatin material, its amount, and the size, shape and functions of the chromosomes themselves. There is yet one more important chromosome constant and that is their number per cell. Not only in the individual but throughout the species is this number very constant, and as all chromosomes are paired we can let $2n$ represent the number per cell: such a cell is termed a *diploid* and the daughter cells formed by meiosis having a chromosome number of n are described as being *haploid*. Sometimes due to errors in mitosis or meiosis or even in fertilization to be described later, the chromatin material may be unequally divided so that more than half of the chromosomes are congregated around one of the poles of the daughter cells. The resulting condition is known as *polysomy* and may be represented by the formula $2n \pm x$, and it is interesting to note that the gene balance is so delicate that it frequently happens that the polysomoid condition is lethal; if however such a cell be viable it results in the establishment of a definite and distinct physiological or morphological variation. When this occurs during meiosis, paired chromosomes passing to the same pole, the phenomenon is termed *non-disjunction*.

It occasionally happens that the separation of chromatids in mitosis, or of chromosomes of homologous pairs in meiosis, fails to take place; the new cell produced thus has a chromosome number of $4n$ in the former case and $2n$ in the latter. It is readily understood that if these germ cells are fertilized we may get a zygote exhibiting the conditions of *polyploidy*, those having $3n$ chromosomes being *triploids*, those with $4n$ *tetraploids* and so on. Polyploids are much more viable than polysomes and this former phenomenon is one of the explanations put forward for the origin of different species, and we can understand how numerous must be the possible variations when we consider the possibility of polysomy superimposed on polyploidy.

Of all the causes of variation enumerated under this heading of chromosome behaviour, gene mutation stands out in that it results in the formation of new and hitherto untried characters which are then submitted to the test of the environment in which the cells may find themselves placed. If these new characters fail to suit the environment the cells will not be able to survive; if they fit, they not only survive but, reproducing their kind, make possible the various combinations and permutations of characters by the other methods described, and thus we see evolution in the new light of modern genetics. Evolution is due to the establishment of variations which fit the environment best: the term survival of the fittest is true only as long as we remember that fitness is not an absolute quantity but is relative to the environment, and the phrase really means the survival of those that fit the environment best, and as the environment changes, so does the type of individuals which are the 'fittest' change also. Evolution according to this conception is thus due to the selection by environmental forces, of those types of organisms that suit the environment the best from amongst the many variations that gene mutations present to it. Nature's plan whereby life may be continuous whatever be the environment, is prolific production with enough mutants to ensure that some at least may be found suitable. The other causes of variation such as polysomy, non-disjunction etc., are note-worthy owing to the fact that they do not introduce any totally new characters into the cell, but merely modify or re-arrange already existing groups of characters by quantitative gene alterations. They bring about variations in quantity of those qualitative changes already tested and tried and found useful, and hence these changes are generally relatively advantageous. The establishment of these new variants depends greatly on hybridisation which brings us to the third great factor in variations, the method of sexual reproduction which we shall now discuss.

(*c*) *Sexual reproduction*. Very early in the embryonic development of the human, undifferentiated cells are set aside for the formation of the sexual glands and these remain undeveloped until puberty when, under the action of internal secretions, they take on their adult structure and functions, one of the latter being the production of germ cells. In the male this production is known as *spermatogenesis* (Figure 5) and the male gametes are found to be derived from cells known as *spermatogonia* which are present in the layer next to the thin basement membrane of the testicular tubules. These cells undergo mitotic division—the number of successive divisions in man is not known—eventually forming *primary spermatocytes* which are pushed further towards the centre of the tubules. Each primary spermatocyte then forms two *secondary* *spermatocytes* by meiosis, each of these therefore having only half the chromatin material of its parent primary spermatocyte. Each of these new cells then divides by mitosis into two *spermatids* which become attached to the nurse cells or cells of Sertoli in the tubule walls. The chromatin material collects in the spermatid near the point of attachment to the nurse cell, while the cytoplasm congregates towards the free pole and thus gradually by a structural or morphological change does the

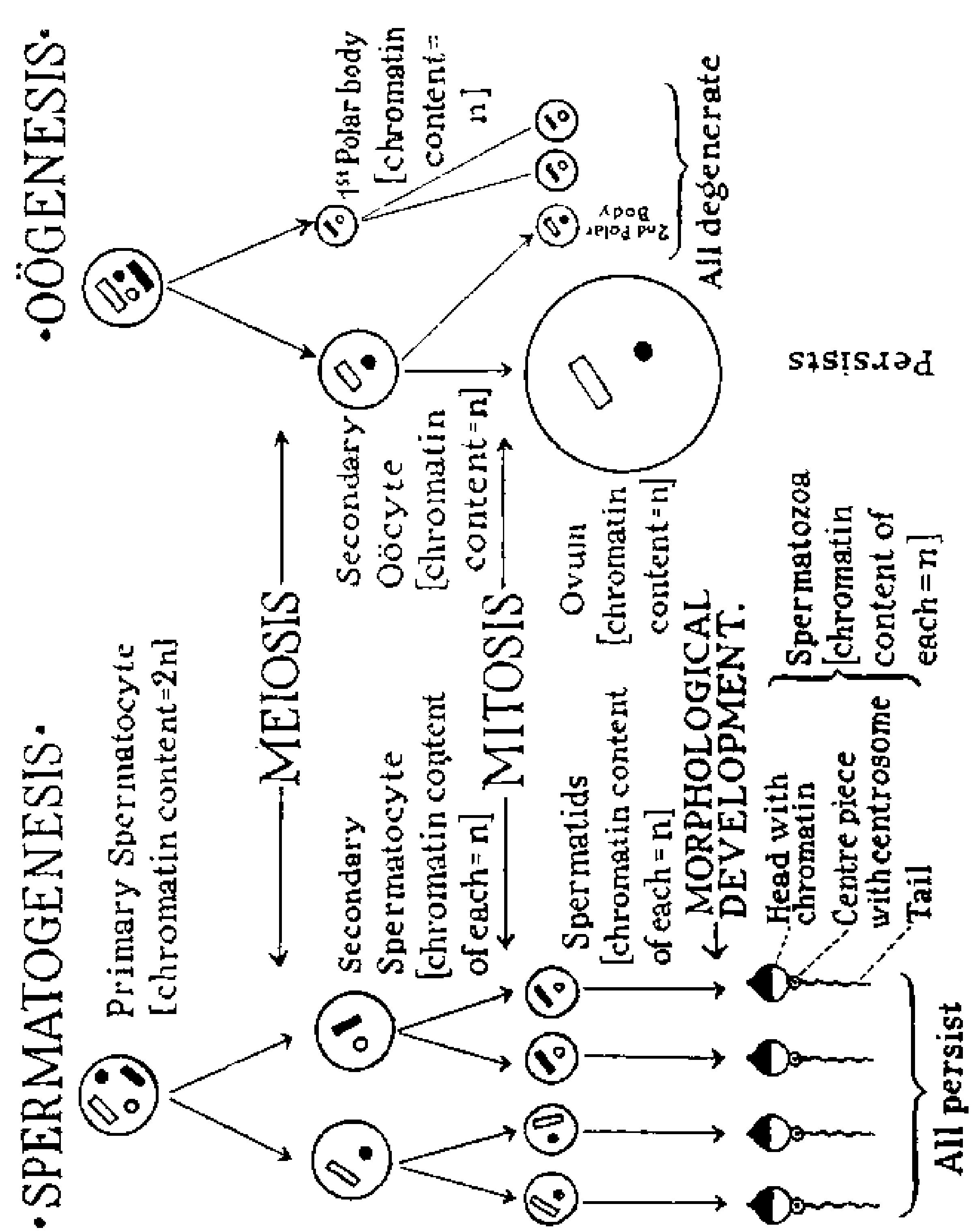


Figure 5. Diagramatic comparison of spermatogenesis and oögenesis. Two pairs of chromosomes are represented as being present in each case, the pairs being differentiated by the shape, and each chromosome of each pair by black or white.

spermatid develop into the young *spermatozoön*, or functioning male gamete, which consists of a head containing all the chromatin material, a middle piece containing the double centrosome, and a long filamentous tail representing all that is left of the cellular cytoplasm, and providing the mobile mechanism of the cell.

Oögenesis (Figure 5) or the production of ova, is a very similar process. An *oögonium* divides by mitosis forming *primary oöcytes* and each of these by meiosis gives rise to two cells of unequal size, one a *secondary oöcyte* and the other the *first polar body*. The inequality of size is due to the fact that practically all the cytoplasm passes into the oöcyte. The polar body may further divide but it soon disintegrates, while the oöcyte divides, this time by mitosis, but again unequally into an *ovum* and a *second polar body* which ultimately suffers the same fate as its first namesake. The significance of this polar body formation may well be that all the cytoplasm of four cells is reserved for one--the ovum, whose main characters are a nucleus with half the chromatin material characteristic of its species and a very large amount of cytoplasm.

The process of gamete formation in the two sexes differs therefore in these two main respects (*a*) four functional male gametes are formed from each primary spermatocyte whereas each primary oöcyte yields only one mature ovum, and (*b*) the cytoplasm in the sperm is minimal and is specialised for locomotion and in the egg it is maximal and specialised for attraction of spermatozoa and for the manufacture of food yolk.

With the process of *fertilization* we get fusion of the nuclei of the male and female gametes which, except in parthenogenesis, provides the necessary stimulus for the egg to develop into another individual. The fertilized egg is known as a *zygote* and there are two important things to notice about zygote formation (*a*) that by the fusion of two haploid cells, the diploid number of chromosomes characteristic of the species is restored and (*b*) that every zygote has received half its chromosomes from its maternal, and half from its paternal gamete.

The former is only possible if meiosis had taken place somewhere during the germ cell formation and in fact it was due to Weismann reasoning that this must happen, that meiosis or "reducing division" as he called it, was first discovered. Meiosis as we have seen gives the opportunity for the reshuffling of the genes and their redistribution between the members of chromosome pairs, but only in one individual; for if the two cells formed by meiosis could reunite in zygote formation, no new gene combinations and hence no new genetic characters would appear in the new cell.

In zygote formation by the sexual method (or *amphimixis* as it is called) however, opportunity is given for totally new pairings of factors from different individuals and hence for the appearance of new characters in the next generation. Should the characters thus developed be advantageous, they can be kept more or less intact by inbreeding—as shown in the breeding of pedigree animals—or if not, new combinations can be tested by further cross-breeding.

It is thus seen that although chromosome behaviour in mitosis and meiosis provides opportunities for rearrangement of differing factors brought into existence by mutations, it is sexual reproduction that is the important mechanism whereby the characters due to varying combinations of these factors are given an opportunity to show their worth in the environment in which we live.

It is perhaps fitting to conclude this aspect of genetics by drawing attention to the fact that the body does not manufacture germ cells. The old time-honoured problem concerning the hen and the egg is based on the fallacy that either the hen must produce the egg or the egg must produce the hen. The former is certainly not true, and the latter is only a half truth. The egg produces the hen plus other eggs, or the cock plus its sperm. It is the property of the germplasm to be able to produce not only more germplasm but also somatoplasm; a germ cell gives rise to other germ cells plus body cells, and the latter form the temporary housing and provide the protection and nourishment necessary for the germ cells till they, meeting another germ-cell line, form another zygote which develops its own body. The body thus hands on to the next generation, not a germ cell of its own making but a germ cell of the parent line which has been entrusted to it and which it has nourished and protected for a brief space of time, and having nourished and protected it, and having passed it on, its duty is done and it perishes. As Conklin has so aptly put it, the body is but the mortal trustee of an immortal substance.

Life is thus the exemplification in discontinuous somata of germinal continuity, a wonderful example of union of two parties for their mutual benefit, the germ line receiving the protection and nourishment necessary for its continuity, and the body receiving the factors from the germ line in such a way that it may develop characters best suited for its function as a trustee.

In reviewing the evidence brought forward in this article two things stand out in relief; they are (*a*) that the more histological technique helps us to probe chromosome behaviour during cell division, the more satisfactorily is this theory found to explain genetic data and (*b*) that when one contemplates the ingenious and multiple mechanism for the production of variations the amazing riddle of heredity seems to be, 'how can we explain the fact that children are so like their parents?' rather than 'how can we explain their variations?'

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Review of Books

MANSON'S TROPICAL DISEASES.

Edited by

P. H. Manson-Bahr, D.S.O., M.D.

Tenth Edition, Demy 8vo (8¼ × 5⅜ ins.), 1,004 pages, with 22 colour plates, 15 half-tone plates, 381 figures, 6 maps and 38 charts. 31s. 6d. Cassel.

Six years have elapsed since the last edition of this standard work on tropical medicine. The notable advances in the fields of rickettsia and virus diseases that have taken place during this period are adequately dealt with. In the present edition there is a greater concentration on the clinical aspects with a corresponding reduction in the amount of space previously given to medical zoology. This is to be commended as the latter subject is now-a-days adequately dealt with in the many text books devoted to the subject, and has grown too wide not to render special books necessary for the serious student. Most zoological facts required by the clinician will however be found in this edition.

The volume maintains its previous excellence in the matter of plates, illustrations and letter-press. The one misprint we noge 149, when Forkner's name was misspelt. The book is one no clinician practising in warm climates can afford to be without.

Acknowledgements.

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