

MEDICO, SUPERNATURAL SUGGESTIONS

VOL - IX

NO. 8

AUGUST 1940

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# MEDICO-SURGICAL SUGGESTIONS

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A MONTHLY JOURNAL OF PRACTICAL MEDICINE & SURGERY  
Editor: Dr. P. R. Venkappaya.

VOL. IX

AUGUST 1940

NO. 8

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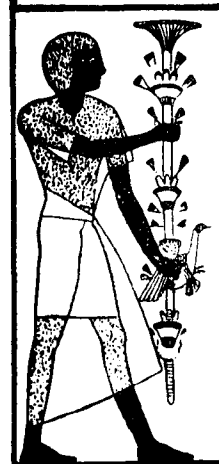
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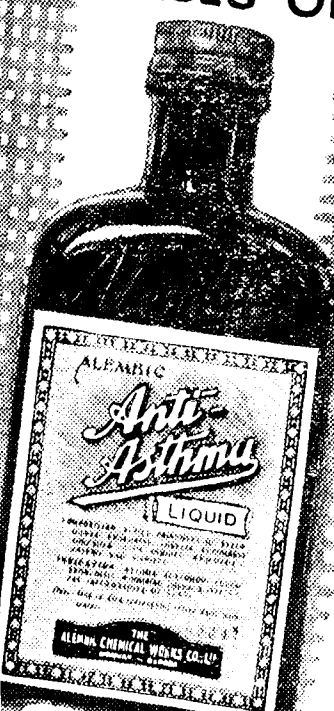
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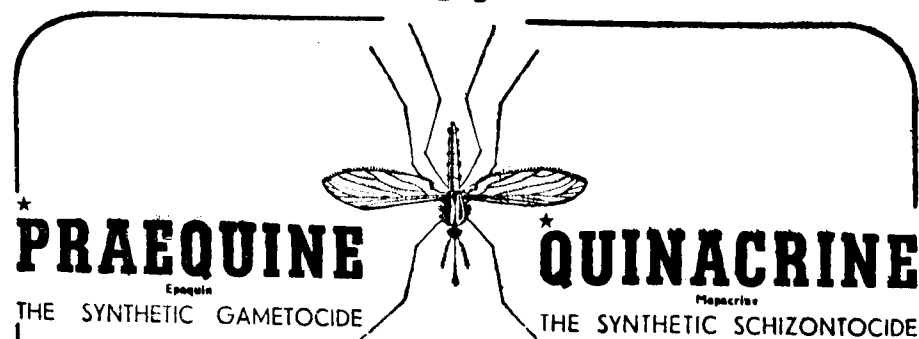
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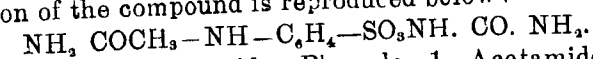
## Original Articles.

### U. S. T. IN MALE GONORRHOEA.

(A Preliminary report)

BY B. N. GHOSH, D.Sc., (LOND.) P.R.S. (CAL.) AND A. C. DEY.  
*Lecturer on Clinical Surgery, A. A. College and Hospital, Calcutta.*

We will endeavour in the following lines to discuss in detail the experiences gained so far on urea sulphazide—'T' (U.S.T.), a recently introduced sulphanilamide compound, in the treatment of gonorrhoea by the oral route. For the sake of clarity the chemical composition of the compound is reproduced below:—



Chemically it may be said as Phenyle—1—Acetamido—4—Sulph—Amidourea. It is sparingly soluble in alcohol and acidulated water, is decomposed by boiling with caustic alkalies.

In the following it will be seen that 17 cases were subjected to U.S.T. course. Although most of these cases were not with acute manifestations, majority of them give history of having contracted the infection recently.

CASE 1:—H. M., 28 years. Duration 3 weeks. Slight purulent discharge from the urethra, pain and burning sensation. U.S.T. 2 tab. T. D. S. for 4 days. Discharge thin and mucoid at the end of the 4th day. Pain and irritation disappeared after 8 tablets or 3 days. Reported reappearance of the purulent discharge after 8 days. Did not submit to any more U. S. T. treatment.

CASE 2:—M.M. 20 years. Duration 6 months. Thin purulent discharge. Occasional burning sensation. U.S.T. 2 Tab. T.D.S. for 5 days. Mucoid discharge from the 4th day. Reported reappearance of the purulent discharge from the 11th day. Did not take further course.

- CASE 3:—H.M. 25 years, duration—1 month. Thin purulent discharge, slight burning sensation. Vague pain over the left knee-joint. U.S.T. 2 Tab. T.D.S. for 6 days. Slight discharge persisted at the end of the course. Pain over knee disappeared. Advised a course of specific vaccine, but refused.
- CASE 4:—H.M. 35 years. Duration—15 days. Yellowish discharge, pain and burning sensation. U.S.T. 2 tablets T.D.S. for 7 days. Pain and burning sensation abated from the 4th day. Slight discharge at the end of the course. Smear examination revealed a few gonococci.
- CASE 5:—H.M. 42 years. Duration 22 days. Thin purulent discharge. Pain and burning sensation. Pain over the left knee and elbow joints. U.S.T. 2 tab. T.D.S. for 7 days. Pain and burning sensation abated from the 4th day. No discharge at the end of treatment. In this case specific vaccine in small doses was given daily for 6 days after the course. Discharged cured. Did not report further.
- CASE 6:—H.M. 34 years. Duration 18 days. Purulent discharge. Burning sensation and pain during micturition. U.S.T. 2 tab. T.D.S. for 5 days. Thin discharge present. Pain and irritation nil. This patient did not complete the course and left treatment all on a sudden.
- CASE 7:—H.M. 21 years. Duration 9 days. Usual manifestations of Urethritis. U.S.T. 3 tab. T.D.S. for 7 days. Pain and irritation disappeared from the 5th day. No discharge at the end of the course with a negative smear.
- CASE 8: H.M. 28 years. Duration 11 days. Thick discharge. Pain, burning sensation. A feeling of general depression. U.S.T. 3 tab. T.D.S. for 7 days. Janet irrigation with pot. Permang. (1 in 5000) for the first 3 days. Discharge thinned out from the 4th day. No discharge at the end of the course. Negative smear.
- CASE 9:—H.M. 24 years. Duration 12 days. Abundant thick discharge. Extreme pain and irritation. Chordee. A feeling of general depression. U.S.T. 3 tab. T.D.S. for 7 days. Janet irrigation with pot. permang. (1 in 10,000) twice daily during the first 4 days. Mist. pot. brom. for the first 3 days. Pain and irritation less from the 4th day. No painful erection after 3rd day. No discharge at the end of the course. No gonococci detected in smear.
- CASE 10:—M.M. 18 years. Duration 7 days. Thick discharge and usual symptoms. U.S.T. 3 tab. T.D.S. for 7 days. Concurrent Janet irrigation with pot. permanganate (1 in 10,000) once a day for the first 5 days. No discharge and symptoms at the end of the course.

- CASE 11:—H.M. aged 23 years. Duration 12 days. Abundant thick discharge. Scalding pain on passing urine. Lips of the meatus swollen, constitutional disturbances e.g. fever, constipation etc., present. U.S.T. 3 tablets T.D.S. for 7 days. Janet irrigation with pot. permanganate (1 in 10,000) with small doses of vaccine for 4 days after U.S.T. course. No discharge and no symptoms at the end of treatment.
- CASE 12:—H.M. aged 22 years. Duration—16 days. Thin purulent discharge and usual manifestations. U.S.T. 3 tab. T.D.S. for 7 days. No symptoms and smear free from gonococci at the end of the course.
- CASE 13:—M.M. 26 years. Duration—2 weeks. Abundant thick discharge and usual pain and irritation. U.S.T. 3 tab. T.D.S. for 7 days. Discharge thinned out but acute pain along the whole of the cavernous portion of the urethra persisted. Specific vaccine in small doses given every alternate day for 3 doses after which the pain subsided. From 7th day after the end of the first course, a second U.S.T. course 3 tablets T.D.S. for 7 days was given. Smear negative.
- CASE 14:—H.M. aged 32 years. Duration 14 months. Thin whitish discharge. Occasional burning sensation. Stricture present. U.S.T. 3 tab. T.D.S. for 7 days followed after a week by a second course. Specific vaccine given in the interval between the two courses. Discharge still persisted, with positive smears.
- CASE 15:—H.M. aged 22 years. Duration—15 days. Thick discharge with usual manifestations. U.S.T. 3 tab. T.D.S. for 7 days. Janet irrigation with pot. permang. once a day for the first 5 days. No symptoms. Smear negative at the end of the course.
- CASE 16:—H.M. 24 years. Duration 9 days. Abundant thick discharge and usual pain and burning sensation. Pain in the left knee-joint. U.S.T. 3 tab. T.D.S. for the first 2 days. 3 tab. on the 3rd day total 21 tab. Pause for 4 days. 2 tab. B.D. on the 8th day, from the 9th to the 15th day 2 tab. T.D.S. Total 67 tablets. Small doses of specific vaccine 4 days during the interval period. Smear negative at the end of the course.
- CASE 17:—M.M. aged 24 years. History of 12 days. Before being attended by one of us (Dey) this patient had a short course of treatment by one of his friends, who while irrigating the urethra broke his glass syringe and caused one wound on the meatus which was found to be

covered with thick slough. This patient had paraphymosis and the usual manifestations of urethritis. U.S.T. was given 3 tab T. D. S. for 7 days. Smear examination revealed no gonococci but only a few pus cells. The cause for the presence of the wound on the meatus was still slightly present.

#### DISCUSSION ON DOSAGE

At the commencement of trials the dose administered was 2 tablets (gr.  $7\frac{1}{2}$  each) T.D.S. for four, then five, and then six rising to seven days. Finally a standard dosage of 3 tablets T.D.S. for 7 days (63 tab.) was reached. An explanation is perhaps necessary for this variation in dosage and length of treatment. Since it was not possible at the beginning to estimate the exact effective dose and toxicity of the product, it was thought worth while to keep the total dosage as low as possible in order that the toxic manifestations, if any, would be less severe. This insufficient administration perhaps accounts for the re-appearance of the symptoms in two cases (1 and 2) and might have paved the way as well to be resistant to any subsequent sulphanilamide course. But on the other hand it has certainly brought to light that the intensive course of treatment as was advocated later on would not lead to serious toxic manifestations.

#### ANALYSIS OF THE CASES TREATED

The intention from the very start was to exclude as far as practicable all supplementary treatments, particularly in those cases where the symptoms were comparatively straight and simple. Irrigation with pot. permang. once or twice a day or a short course of vaccine were only taken recourse to whenever it seemed essential that an attack from all possible angles was inevitable. Thus in case No. 9 (and some other cases as well) irrigation was deemed necessary as the discharge was abundant and thick. It will have been seen that in none of these cases, the vaccine was administered preliminary to U.S.T. course but was only given in those cases which failed to respond squarely with one U.S.T. course (except case 16).

Case 13, a strongly built pathan was given a full 7 days course the discharge was almost nil but an acute pain along the whole of the cavernous portion of the urethra still persisted. A course of vaccine up to 3 doses was given and at the end of the vaccine course the pain abated and finally the smear was negative with a second U. S. T. course. In the 6th case of this series after the patient had 21 tablets maculo-papular rash appeared on the exposed parts, *e.g.*, palms of the hands. The drug was stopped and a vaccine course was given for 4 days. The rash in the meantime disappeared and from the 8th day U. S. T. was again started with 2 tablets B. D. S. on the 1st and 2nd tab. T. D. S. for 7 subsequent days. In this case a total of 67 tablets were given. The rash which made its appearance in the beginning of the course disappeared on withholding the

drug but did not reappear on subsequent administration. The explanation to this is perhaps that patient admitted of having exposed himself too much to sunlight but stopped doing so later on when warned of such developments.

#### MODE OF ACTION.

It is difficult to assess the 'modus operandi' of U. S. T. but it appears that the drug itself is reduced in the body to some active substance to render it to acquire gonococcicidal action. To achieve this end (like all other drugs) a certain concentration in the blood is absolutely essential which is perhaps reached by a daily administration of 4.5 to 5 grm. of the product.

#### TOXICITY.

For the determination of the toxicity in animals the drug was used in the form of a 5% suspension in water using a suitable suspending agent. It was administered by subcutaneous injections in mice weighing between 15 to 20 grams. The animals were observed for one week and deaths occurring within one week were recorded. By calculation the lethal dose (10) was found to be 5.5 grm. per kg. Turning to the other side of the picture, it is well-known that when a new chemotherapeutic compound is placed for clinical use it is of utmost importance to observe at the outset whether the drug itself has any toxic effects. A study of the cases will show that there is little evidence that U. S. T. is toxic at least as far as its immediate effects are concerned.

#### DISCUSSIONS ON FAILURES.

Coming to the question of failures in this series, it seems worthwhile to consider two main factors :—

(1) Whether the drug itself was below par.

or

(2) Whether the circumstances of the patients were such as to lead to an inevitable failure by such measure.

It is very difficult to draw any conclusion on the first point. As a matter of fact it will be seen in the following lines that there are so many common factors which stand in the way of a successful end result in the treatment of gonorrhœa whatever course of treatment may be adopted. Taking for granted that the gonococcicidal action of the drug was not up to the mark, the question may be asked, why then definite improvements were observed in other cases where no supplementary treatments were done? It would therefore be reasonable to suppose that failures were not entirely due to the inefficiency of the product.

As regards the second point, *i.e.*, conditions of the patients which govern success and failures, Harrison suggests two chief causes of chronicity and relapse :—

(a) Failure to develop an adequate antigonococcal power in the patients' system.

(b) Imperfect drainage of some focus in which the infection still smoulders.

The first point does not come much into consideration as far as treatment with U. S. T. is concerned. It has been claimed that the preparation is effective even before the gonococcal C. F. T. is positive.

Regarding the second, Harrison suggests that he has seen in a substantial number of cases in which after systemic dilatation, irrigation with different chemicals, injection of vaccines and other methods of treatment have failed to show positive results but cauterisation of an oozing spot in the urethra stopped all signs of gonorrhœa.

The view is also maintained by others as well. While on the subject of "Chemotherapy of Gonorrhœa" the B. M. J. editorial (1938) states.

"Complications as a rule clear up rapidly but there is a good deal of evidence that when there is a closed focus—such as litritis or an infected para-urethral duct—failure is frequent, and this may account for any of the relapses." Harrison (1938) thinks that the present chemotherapy is likely to fail in any case where the local drainage is defective. Clark and Branham (1938) raise the question that peri-urethral infection of gonococcal origin has been less favourably influenced by sulphanilamides than prostatitis. This point is interesting in view of the fact that when the action of the drug is *via* the blood why then there should be a variation of action in two different places? The possible explanation according to the writers is that the concentration of the drug when it is excreted in the prostate gland is much higher than which obtains in the glandular structure of the anterior urethra.

When all possible causes of failure in a case of normal environment have been eliminated, the following important factor mentioned in the B. M. J. editorial (1938) comes into consideration "some patients seem to conjugate the drug in their tissues less efficiently than others which may be an explanation of some of the failures."

A study of the above will undoubtedly indicate that failures in chemotherapy of gonorrhœa are not always due to the drug itself as the case may have any of the above reasons to explain their non-response.

#### ON RELAPSES.

On a perusal of the cases it will be seen that two cases only reported themselves for reappearance of symptoms after definite improvements had set in. In these two, the cause of reappearance, as already mentioned, may be that either the dosage was too small to be effective or they were the "early relapse" cases described by Cokkins and McElligot (1939). But the condition goes much more

in favour of the insufficient dosage to account for the reappearance of the original manifestations.

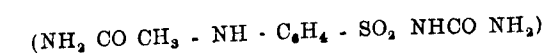
#### CONCLUSION.

Ripley Oddie (1938) asserts that it is as yet impossible to assess the end results of chemotherapy of gonorrhœa with any certainty. It would therefore be unwise to expect a large number of cures but on a critical study of the above it seems that in male gonorrhœa U. S. T. offers the possibility of good cure percentages and a low toxicity. Time will of course be needed for the full clinical evaluation of the product. It would also be of considerable interest if an investigation on the treatment of female cases is made.

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## TREATMENT OF INTRACRANIAL HÆMORRHAGE OF THE NEWBORN

BY J. D. ROY, M. B.

Gopalpur.

Intracranial hæmorrhage of the newborn is a difficult problem which confronts the obstetric practitioner. The condition, not often, threatens the life or usefulness of the infant and constitutes a tragedy to its parents. Besides direct pressure on the child's head, other important etiological factors are the circulatory disturbances resulting from decreased pressure associated with 'cupping'. The passive congestion in the longitudinal sinus always constitute a danger point. There is also the problem of asphyxial stasis and the friability of the blood vessels at birth. Then there is the danger of anoxemia. The site of the lesion, the amount of hæmorrhages and the pathological changes are important factors. Meningeal hæmorrhages often produce little or no permanent change, while hæmorrhages into the substance of the brain are likely to cause death, or if the child survives, grave motor disturbances with or without recurrent convulsive seizures. Petichial hæmorrhages may cause permanent damage through degenerative changes which generally follow. Hæmorrhage into the ventricles is generally massive and practically always fatal.

The manifestations of cerebral hemorrhage may be immediate or they may be delayed for several days or even weeks. The symptoms may be mild or severe. All symptoms are due to pressure and irritation. In the milder group of cases the symptoms are predominantly those of cerebral irritation rather than of greatly increased intracranial pressure. The symptoms of pressure are: generalized or localized convulsions alternating with stupor, cyanosis, bulging fontanel, cerebral cry etc. The symptoms of irritation are: refusal to nurse, restlessness, and occasionally faint twitching of the facial muscles and sometimes irregularity in the respiratory rhythm. The obstetric practitioner should always be on the look out for a potential case of intracranial hæmorrhage. For, early diagnosis and treatment of intracranial hæmorrhage would save many lives and even many more crippling defects. It has been established that small extravasations of blood into the subarachnoid spaces may be absorbed without clot and therefore without cerebral damage.

### TREATMENT.

As preventive, routine and diligent prenatal and antepartum care and careful intrapartum management are recommended. This will to a great extent reduce the incidence of intracranial hæmorrhage of the newborn. The curative treatment consists of (1) control of hæmorrhage, (2) control of convulsions and (3) maintenance of nutrition.

1. *Control of Hæmorrhage*: Intramuscular injection of whole (human) blood, 10 to 20 c.c., into the buttocks is the accepted treatment for this condition. Some obstetricians use whole blood injection as a routine procedure for infants born in difficult labour. Sanford questions the usefulness of this procedure, as according to him "far from aiding coagulation, injection of blood actually prolongs clotting time in these cases". Physical rest is essential in all hæmorrhages, including cerebral. The infant should be disturbed as little as possible. The respiration is practically always found to be irregular, and cyanosis and periods of apnea are present. The administration of carbon dioxide and oxygen by means of nasal catheter relieves respiratory embarrassment and secures rest for the infant. Riesenfeld recommends that the infant should be kept in a "vertical position" for eight to ten days. This is done "by placing the pillows along the sides of the baby, snugly filling the space between the infant and the sides of the crib" (lahr).

2. *Control of Convulsions*: Convulsions are due to increased intracranial pressure as a result of hæmorrhage. If the pressure be high, relief will be obtained from withdrawal of cerebro-spinal fluid by cisternal, or lumbar puncture. Intravenous injection of 25 per cent. glucose solution is of value in reducing the pressure. This may be used alone or in conjunction with cisternal or lumbar puncture. A 15 per cent solution of magnesium sulphate, one ounce, may also be given *per rectum* with the same object in view (Whitla). For birth injury showing "a bulging fontanel, coma, twitchings, or cyanotic attacks, as a result of hæmorrhage", Moncrieff (1934) recommends administration of hypertonic rectal saline. A teaspoonful of common salt in two ounces of water is run in rectally with a fine catheter. The infant's buttocks are held or strapped tightly together for some time, in order to ensure that the saline is retained. By this means "the increased intracranial pressure and cerebral edema are reduced". Rest should be obtained by adequate dosage of sedatives, e.g., chloral, luminal or bromides. Chloral, gr. 2, is given *per rectum* every three of four hours until the child is drowsy. Opiates are better avoided, because of their deleterious effect on the respiratory centre. Intramuscular injection of one or two c.c. of 50 per cent magnesium sulphate is often very helpful in "controlling the intensity of the seizures". Surgical removal of the clot is recommended wherever possible.

3. *Maintenance of Nutrition*: Nursing is an important problem in this condition. Infants with intracranial hæmorrhage are very difficult to feed, because they are either too somnolent or too restless. Maintenance of the strength of these little patients is essential, because many patients at this stage die of insufficient food. They should be adequately fed with human milk, where available. The breast pump may be used and the milk so obtained should be fed

by bottle if the infant is not very weak, or by dropper if the infant is too weak to suckle, or by nasal tube if satisfactory feeding by bottle or dropper is not possible. Care should be taken, however, that the infant is not overfed. Where breast milk is not available, evaporated acidified milk can be administered in concentrated form—thus “affording a high caloric intake in relatively small bulk”.

## ENDOCRINES IN RELATION TO GROWTH IN CHILDHOOD

ISAAC A. ABT, M.D., SC. D. CHICAGO.

Physical and mental growth depend in large part upon certain hormonal glands. There are, however, so many factors to be considered in the process of growth that one should show considerable conservatism in assigning the whole function to any single factor.

(1) The vital elements of hereditary transmission are contained in the chromosomes. The rate of lateral or linear growth and the completed architectural structure of the mature individual are inherent in the chromosomes. Perhaps also mental aptitudes are transmitted through these agents.

(2) Unfavourable environment conditions may alter normal growth and development. Among these factors may be mentioned (a) reduction of oxygen and nutritional material contained in the maternal blood supply; (b) toxic products transferred from the mother to the fetus, or exposure to deleterious conditions after birth; (c) acute or chronic infections of the fetus or the newborn infant; (d) excess or deficiency of the hormones required for normal growth.

(3) Cerebral activity is thought to influence growth processes. Inflammatory foci, degenerative processes or neoplasms in the hypothalamus may cause obesity and transmit impulses through the autonomic nervous system to the pituitary gland, causing hormonal dysfunction and growth disturbances. There is clinical evidence that disease in the hypothalamus may influence the specific secretions of the pituitary gland. An example of hypothalamic dysfunction is the condition known as dystrophia adiposogenitalis, or Frohlich's syndrome, in which obesity, sexual infantilism, increased sugar tolerance and mental hebetude may occur. Recent studies incline to the view that Frohlich's syndrome is caused by a lesion in the hypothalamus, rather than by primary dysfunction or disease of the pituitary gland. Abnormal adiposity occurs in certain hypothalamic disorders which are not associated with any demonstrable involvement of the pituitary gland.

(4) Interrelationships between various endocrine systems certainly exist. For example, it is assumed that there is an intimate relationship between pituitary and thyroid. However, the finer details of endocrine interaction are not definitely known.

(5) Defective nutrition due to infections or disturbances of metabolism may affect growth adversely. It is recognized that congenital heart disease, dysfunction of the liver, interstitial nephritis, tuberculosis, syphilis and other acute and chronic infections may retard growth.

(6) A deficiency of vitamins may retard growth.

A hormone may be defined as a chemical substance produced in an organ which under normal conditions, being carried to another organ by the blood stream, excites in the latter organ some form of functional activity.

The effect of hormones on the growth and development of the fetus is an interesting point in our discussion. During the period when the fetus is growing most rapidly, the internal secretory glands are not yet functioning. In the latter months of intrauterine life some of the endocrine glands begin to secrete the active principle in minimal amounts. Numerous observations support the view that the mother is supplying the hormones required for fetal growth. It is believed that infants in utero store up in their bodies growth hormones derived from the mother. For example, an infant destined to show clinical evidence of hypothyroidism does not usually present symptoms at birth. It is only later when the stored up active principle of the thyroid gland derived from the mother has been exhausted that manifestations of hypothyroidism appear.

Sex hormones are found in the newborn infant which are undoubtedly of maternal origin. It is supposed that they give rise to the so-called “pregnancy reactions.” Ovarial and anterior pituitary hormones have been found in the urine of newborn babies until the fourth or fifth day after birth. Pregnancy reactions occur in both sexes. In the female infant these reactions are made manifest by the edematous, spongy and hyperemic vagina and vulva. In addition, the labia are swollen and there may be a discharge of bloody mucus. Pregnancy reactions in newborn male infants are said to be manifested by the discharge of small blood clots from the urethra. Hematuria has been observed, thought to be due to a hyperemic state of the prostate gland. Temporary hydrocele and enlarged testes are sometimes observed. The mammary glands enlarge in both sexes after birth. Von Jaschke believed that 95 per cent. of newborn infants secrete milk. It has been thought that the milk secretion ceases when the sex hormones are eliminated from the infant's body.

It has been assumed also that the hormones which produce the reactions of pregnancy above cited are derived from the estrin of the

human placenta. Estrin, an ovary-stimulating principle, has an action similar to the gonadotropic principle of the anterior pituitary lobe.

*Relation of Vitamins to Hormones.* There is such a mass of evidence at hand to prove that vitamins are necessary factors for growth that one is led to inquire what is the specific effect of each on growth and what relationship, if any, exists between vitamins and hormones. The following assumptions may be stated:

Vitamin B deficiency may cause colloid goiter in rats. Sure and Buchanan found that pure crystalline vitamin B given to albino rats is antithyrogenic. Sure also found that vitamin A deficiency caused a 40 per cent. weight increase in the pancreas, and that in vitamin B<sub>1</sub> deficiency marked hypertrophy of the thyroid and adrenals, and hypertrophy of the pituitary, occurred. On the other hand, avitaminosis caused a marked atrophy of the thymus; this is particularly true of vitamin B deficiency.

Certain vitamins are prepared by synthetic processes in the body and are thus made available for nutritional purposes. Vitamin A is formed in the liver by the splitting of carotene. In the performance of this function does the liver become a hormonal gland? Under the influence of ultraviolet rays, vitamin D is formed in the skin.

Attention has been called to the fact that the same substance may act as a vitamin in one species and as a hormone in others. Vitamin C is ingested with food by man, monkeys, guinea pigs and rabbits (and is thus a vitamin), but is synthesized in the bodies of chicks, rats, mice, dogs and various other animals, resembling the production of hormones.

Animals deprived of vitamin A cease to grow. It is not known whether the vitamin bears any relation to the pituitary hormone which regulates growth.

Similarly, infants may be retarded in growth when the administration of vitamin B is deficient. A sufficient supply of B especially favors growth. Vitamin C is also said to stimulate growth. Rickets due to vitamin D deficiency may lead to deformities of the spine or lower extremities, eventually causing diminution of stature.

*Internal Secretion and Growth.* The endocrine glands of infancy and childhood are of fundamental influence on growth processes. The glands which have to do with growth and development are the hypophysis, thyroid, the suprarenal gland, the pineal gland and the thymus. The parathyroid glands and the pancreas are more indirectly concerned in the growth process.

*The Pituitary Gland (Hypophysis).* It has been said that the chief function of the pituitary is not only to produce its own hormones but also to regulate the production of hormones in other endocrine glands. The hormones of the anterior lobe of the hypophysis influence skeletal growth. Acromegaly, gigantism and dwarfism are

clinical conditions depending upon dysfunction of the pituitary gland. The removal of the anterior lobe of the pituitary in tadpoles caused retardation in growth and failure to undergo normal metamorphosis. Evans and Long proved that the anterior lobe produced growth-promoting hormones. They obtained a saline or alkaline extract of this active principle. This extract, injected intraperitoneally into young rats caused striking increase in growth. Animals so treated attained twice the size of their litter mates. Giant rats can be produced by the injection of the saline extract of the anterior lobe. Injection of this hormone into hypophysectomized animals produced normal growth processes. Evans isolated a purified white powder from the saline extract, the injection of which caused regular increase of growth in female rats. Recent investigations have suggested that growth is not caused by a single hormone but by the combined action of several substances obtained from the anterior lobe. The results of the treatment seem better when the anterior lobe extracts are not fractionated too highly.

*Acromegaly.* Overactivity of the anterior lobe may produce acromegaly, a condition occurring mostly in adult life, characterized by overgrowth of the bones of the hands, feet and face. In true acromegaly an adenomatous tumor composed of acidophil cells is found in the anterior lobe. The disease is rarely found in children, though if it does occur, the stature is enormously increased. However, after the epiphyses have united, further growth in height is no longer possible.

*Gigantism.* This condition is due to a pituitary lesion similar to that which occurs in acromegaly, but gigantism occurs in children when the epiphyses are ununited. Such patients become abnormally tall and the limbs are excessively long.

*Dwarfism.* If hypophysectomy is performed on a rat or dog, dwarfism is observed in the young animal, though in the adult animal a general cachexia occurs, producing a condition resembling so-called Simmonds disease. Deficient production of the anterior growth hormone in the human leads to arrest of growth. One group of miniature individuals is known as the Lorain type of dwarf, and is one of the best examples of hypopituitarism without obese tendencies. As a rule, the limbs are proportionate to the body, and they are symmetrical. The bony structure is light and sexual development is retarded. This type of dwarf is usually of normal intelligence and the appearance and facial expression are not unattractive. In some the head is relatively large in proportion to the body.

The dwarfism which results from hypothyroidism will be mentioned later. Aside from the endocrine factors in growth retardation, there are other causes of dwarfism not related to hormonal

action. Among these may be mentioned achondroplasia or chondrodystrophy, and inflammatory or degenerative disease of bones, as well as the deformities of rickets, osteogenesis imperfecta, and Pott's disease. These latter conditions result in a reduction in stature, though maturation is not, as a rule, affected. Dwarfism may also occur in celiac disease, manifested by chronic intestinal indigestion, osteoporosis and delayed growth of bone. There is retardation of growth in so-called renal rickets, which is a condition manifested by softening of the bones and rachitic-like deformities associated with chronic renal insufficiency due to double hydronephrosis, congenital cystic kidneys or chronic interstitial nephritis.

*Treatment of Growth Disturbances Due to Anterior Lobe Pituitary Dysfunction.* Pituitary dwarfism should be treated early, before the epiphyses are sealed. It is not easy to determine at an early age whether a baby is simply retarded in growth because of nutritional disturbances, or whether the condition is due to a glandular deficiency. There are a number of anterior pituitary growth hormone preparations furnished by the bio-chemical manufacturers. The oral administration of these hormones is usually ineffective. They should be given hypodermically, preferably in doses of 1 to 2 cc. daily, or on alternate days. There is clinical evidence at hand indicating that the growth-stimulating preparations are potent in stimulating growth in experimental animals and in humans. In addition to the specific treatment an adequate diet should be supplied, including concentrated vitamins of A and D and vitamin B, and the vitamin B complex.

*The Thyroid Gland.* When the thyroid is completely removed in young rabbits, it is found that growth is retarded, the animals remain small, they may develop deformities of the front feet and curvatures of the spine, they become drowsy and disinclined to move. The heart rate is slow, the blood pressure is low, and the basal metabolism is decreased. The same results are obtained in other animals. In the human, thyroid insufficiency leads to diminished metabolism and retardation of physical and mental growth and development. Some of the conspicuous changes noted in childhood are the peculiar swollen appearance of the skin, which is also dry and cold and sallow or yellow in color. The nails and teeth are brittle, perspiration does not occur readily, the hair is coarse and short and tends to fall out, the body temperature is usually below normal, the teeth erupt slowly and decay early, obstinate constipation is frequent, anemia is usually present, the voice is inclined to be hoarse and husky. Apathy and low intelligence are observed and growth is retarded. Few of these patients attain normal stature.

R. G. Hoskins remarks that a moderate degree of thyroid insufficiency is fairly common, but is frequently overlooked. He

thinks that in these children mental alertness and intelligence are frequently below the normal level. In children in whom deficiency is present, x-ray pictures of the bones show that there is lack of growth at the epiphyseal junctions, and great delay in the development of the centers of ossification. The appearance of the nuclei of the carpal and tarsal bones may be delayed until the tenth year, and the epiphyses of the long bones may not unite until the twentieth or thirtieth year. This condition is treated by the administration of the dried thyroid gland substance. The required dosage can not be stated for each individual, though one should start with minimal daily doses, the size of which should be slowly and cautiously increased, until an effect is obtained. It is far from desirable to give a dosage sufficient to produce the full physiological effect. The size of the dose should be diminished, if restlessness and increased pulse rate occur. Continued overdosage may cause thyrotoxicosis. The cretin or the hypothyroid individual requires constant observation and treatment throughout life.

*The Thymus.* Gudernatsch fed tadpoles with thymus gland substance and found that these larvæ grew faster than those controls fed on a usual meat and vegetable diet. Those that were fed thymus gland remained in the tadpole stage for a shorter time than those fed the usual diet. Later he fed rats on thymus substance and found that the successive generations showed an increase in the rate of growth, improvement in vitality and longer life spans. Leon Asher in 1915 obtained a water-soluble extract from the thymus gland which he called thymocresine. When this substance was injected into rats, acceleration of growth was observed.

Rowntree, Clark and Steinberg used an extract prepared from the calf thymus by Hansen (1930). They found that, if this substance was injected into rats, the third generation of these animals showed an increased rate of growth, which was further accelerated in succeeding generations. The experimental work on the thymus thus far has been performed on small animals, though as is frequently the case, results thus obtained cannot be literally translated into pharmacological reactions in the human being. In a few instances thymic tumors seem to have caused precocious growth and development.

*The Pineal Gland.* Rowntree and his associates experimented with an extract of pineal gland prepared by Hansen. It was shown that, if the substance was injected into rats, these animals became more dwarfed each succeeding generation. These experiments do not as yet clarify the function of pineal gland activities in man.

*The Pancreas.* It was formerly thought that a diabetic child on a well-controlled diet either grew normally or slightly in excess of the average rate. Julian D. Boyd and A. H. Kantrow believe that retardation of growth in children due to diabetes may be prevented

or corrected, if glycosuria is suitably controlled by the administration of insulin and the diet properly regulated.

*The Adrenal Glands.* Hypersecretion of the adrenal cortex may produce stimulation of the sex glands, or possibly influence the anterior pituitary primarily, and the sex glands secondarily. Hypersecretion, particularly of the cortical substance, may produce abnormal hairiness, increase of subcutaneous fat, increased thickness of the upper layers of the skin and enlargement of the sex glands. Hypersecretion of the adrenal cortex tends to stimulate bodily growth and produce individuals of large stature, and with strong, well developed muscles. These persons are usually very alert and mentally precocious. The male child may show increase in the size of the sex organs, whereas the female may show large breasts and excessive growth of hair, and menstruation may occur very early. Aside from the treatment of Addison's disease with extracts from the cortical substance of the gland, it has been suggested that these extracts may also be administered to those suffering from hypoadrenal dysfunction, such as is noticed particularly in the severe prostration associated with diphtheria, pneumonia, surgical or traumatic shock, or peripheral vascular failure. However, the diagnosis of hypoadrenia may be difficult, and the administration of these remedies is more empirical and speculative than of proven value. The therapeutic use of epinephrine and its pharmacologic action as a vascular stimulant are well known.

The attempt has been made to review briefly some of the important facts in the relation of hormones the bodily growth and development. The therapeutic value of a few of these hormonal remedies has been proved to be effective in the treatment of some clinical conditions in man. Treatment with other hormonal extracts is still in an experimental stage. Progress in the study of substances derived from endocrine glands is proceeding rapidly, and we may confidently expect that new and important revelations concerning their isolation and therapeutic application will be discovered in the course of time.

(*Illinois Medical Journal Feb. 1940.*)

## SEDATIVES.

CHARLES A. RYMER, M. D. DENVER.

In a symposium such as this the question of sedatives stands in a unique position. This is so because the advertising claims are often directed to the profession, whereas in the case of cathartics, cosmetics, blood tonics, and tobacco the claims are directed to everyone's attention. Furthermore, the majority of pharmaceutical houses make some effort to check the claims for their product by biological assay whereas this is generally not true of the other products being considered in this symposium.

However, this biological assay gives the physician a false sense of security in that he feels the product is "tested" and accordingly comes to rely upon the manufacturers' claims. Actually this test is for certain pharmacological properties and too often bears little or no relation to clinical use, especially prolonged use. Without entering into a detailed and specific counter charge of the claims made by the manufacturers, which they would promptly contest, it is evident that many of these claims are not supported by subsequent clinical facts. It appears that a careful consideration by each physician of the properties of sedatives and indications for their use might do much to make him independent of advertising claims.

Sedatives include any drug which has a depressant action upon the central nervous system. These drugs fall into four large classes as follows: (1) hypnotics or drugs that induce sleep by acting upon sensitive centers in the mid-brain; these include the barbituric acid derivatives, chloral hydrate, paraldehyde, sulphonol, and ethyl alcohol; (2) sensory depressants such as the opium derivatives; (3) motor depressants, such as the bromides; and (4) aromatic analgesics, such as the salicylic acid derivatives. Thus, we see that while the term sedatives and hypnotics are often used interchangeably, hypnotics are only one group of sedatives.

Certain proprietary sedatives widely and intensively advertised through newspapers, posters, and radio, are sold in huge amounts to the public. Thus, large quantities of bromides, hypnotics and aromatic analgesics are consumed daily, although there is no rational indication for their use. Too often these drugs are used as a crutch for the unstable personality. Uniformly there is little relation between the advertisers' claims and the medical facts. A discussion of these proprietary sedatives would require far more space than is at our disposal. Accordingly, we shall limit the rest of our discussion to a consideration of the hypnotics, especially as prescribed by the physician.

Certain properties should be insisted upon in a hypnotic. These properties are as follows: (1) The drug must produce a reliable hypnotic effect. (2) The hypnotic action must be produced without a preliminary stage of excitement. (3) The drug must not irritate the stomach. (4) The drug must be absorbed readily, so that the hypnotic action is produced at a regular interval after the administration of the drug. (5) The drug must either be broken down in the body or else be excreted rapidly, so that it produces no after effects and does not produce cumulative poisoning when taken daily. (6) The drug must not produce dangerous side reactions, such as cardiac depression. (7) There must be a sufficient margin of safety between the dose required to produce hypnosis and that which produces medullary depression. (8) The drug must not produce tolerance nor a drug habit when given regularly over long periods. While no drug contains all these properties, such claims are made for each new hypnotic as it appears on the market. It is only after years of trial and error that the disadvantages are fully noted.

Needles to say, hypnotics should not be prescribed for the relief of pain. However, they may be combined with the analgesics—such as acetylsalicylic acid, aminopyrine, and acetphenetidin—with good effect. In addition, hypnotics are not effective in the production of surgical anaesthesia because they are not effective as analgesics and also because the anaesthetic dose is as high as 50 to 75 per cent of the lethal dose.

Chronic intoxication from prolonged administration of any hypnotic may result in the following symptoms: gradual loss of ambition; impairment of capacity for concentration; increased desire to sleep; vertigo; ataxia; nystagmus; speech defect; paralysis of limbs; parasthesias; reflex alterations; failure of memory with slowness of thought; albuminuria; muscle cramps; hematuria; porphyrin in urine; and confusion. If administered over a long period of time there is a danger that the patient may come to rely on the drug. Even temporary administration may result in undesirable side reactions such as headaches, nausea and diarrhoea, skin eruption, depression of respiration and circulation, alimentary canal irritation, cardiac and brain tissue damage after their use.

Once taken into the body the hypnotic must be eliminated. The elimination of any hypnotic is dependent upon its degree of fixation by the body, its rate of destruction in the body, and its form of elimination. Barbiturates with an allyl radical are relatively stable compounds, whereas those with a cyclic radical, such as evipal, are unstable and easily decomposed with the body. Other hypnotics such as paraldehyde and ethyl alcohol are rapidly broken down and thereby produce rapid sedation. While chloral hydrate is not broken down in the body it is changed into urochloric acid and excreted as such, thus preventing any cumulative effects. It is one of the most

useful and cheapest of all hypnotics. On the other hand, sulponal is excreted slowly and unchanged, thereby increasing the cumulative possibilities. Its hypnotic effect is postponed for several hours.

The use of hypnotics in insomnia is greatly abused. Sleeplessness is a widespread complaint so persistent and annoying that it creates a formidable part of every physician's practice. Too often the physician has neither the time, ability, nor interest to solve the problem of insomnia and falls back upon one of the hypnotics claimed to be harmless. Perhaps even more often, the patient, having failed to get relief, takes one of the proprietary remedies recommended by a friend, relative, radio or newspaper. However, certain conditions are clear indications for the administration of hypnotics. According to Grabfield these are:

1. When sleeplessness can be foreseen as a result of an acute situation of short duration, such as a tragedy within a family, or the first night in a strange surrounding, etc.
2. When wakefulness is clearly due to an obvious cause, and symptomatic relief will aid in the treatment. For example, discomfort from physical cause such as dyspnea, frequency, diarrhea, itching or any symptom which forces itself into the sensorium.
3. When the cause is unclear but relief is urgently demanded and there is no danger of masking night symptoms.
4. When the sleep mechanism is reversed as in cerebral arteriosclerosis. The use of a soporific endeavors to change the mechanism without intensifying it.

In many cases, however, the cause of the insomnia appears to be on no clear-cut basis. In such cases the sleeplessness appears to be due to no underlying overt stimulation. The sufferer has difficulty in going to sleep; he awakens early and cannot sleep again; or he has periods of wakefulness in the middle of the night. According to Grabfield, the insomnia may be due to faulty habit formation, acute emotional disturbances, or as a past manifestation of a psychoneurosis. Karnosh indicates that one of the immediate causes of insomnia is an anxious preoccupation, such as great concern over health, the repercussion of bitter family scenes, reflection on sexual inadequacy or infidelity, contemplation of business reverses and various other frustrations of the ego. Further, he feels that approximately one half of all persons with chronic insomnia are psychoneurotics. It is axiomatic that the treatment of any symptom should be directed to its cause, and since the psychoneurotic so frequently suffers from insomnia, it is obvious that treatment must be directed against the underlying condition.

In the case of insomnia due to faulty habits of sleep a hypnotic should be used rarely and then only as a temporary palliative. In the case of acute emotional disturbance, the continued use of any hypnotic is potentially dangerous, both from a physical and psychic

point of view. The psychopharmacology of the barbiturates is not well known, and prolonged use of these drugs in patients with personality difficulties often results in further confusion and accentuation of the problem. Therefore the recommendations frequently made by advertisers that their product be used in cases of hysteria, neurasthenia, "nervous insomnia" "mild anxiety," cardiac and gastric neuroses, listlessness, irritability, "highly nervous tension," "psychoses and various types of neuroses," "insomnia due to emotional strain and nervous instability" are to be condemned. Medical facts are wanting to support the claims that these conditions are aided by such medication. The tragic fact is that many cases of barbituric acid poisoning and bromide intoxication are seen daily because too many physicians attempt to treat the patient pharmacologically, and are too willing to accept advertisers' claims as medical facts.

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## IMPORTANT NOTICE

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# MEDICO-SURGICAL SUGGESTIONS

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## Editorial.

### ARTIFICIAL FEVER THERAPY.

The artificial production of a high temperature is a valuable aid in the treatment of certain diseases and is more and more coming into frequent use in the present day. It is a common observation that an intercurrent fever helps to alleviate the symptoms to gonorrhoeal urethritis. Similarly symptomatic relief is obtained when a sufferer from arthritis gets an attack of influenza. From such experiences, one is led to expect relief from disease by producing fever by artificial methods, and the results of clinicians all over the world amply justify these expectations.

One of the earliest attempts at artificial fever therapy was done in 1918 by Wagner von Jauregg, who treated cases of general paralysis of the insane by the injection of malarial parasites. This epoch making discovery won for him the Noble prize, but left in its train the baffling problem of severe and uncontrollable reactions. Injections of foreign protein such as aolan, milk, and T.A.B. vaccine are used more frequently, and the degree of fever could sometimes be regulated more or less by varying the quantity of protein injected. But even here, a severe reaction sometimes ensues, and the physician has to be on the alert to ward off any untoward and unexpected complications.

A further advance over these methods is the induction of fever by electrical methods—electropyrexia. High frequency diathermy, electromagnetic induction, and ultra-short waves are the usual methods used. Any of these methods permit the application of heat to the tissues, either locally over small areas of the body or over the entire body. The use of a radiant heat lamp should also be mentioned for the sake of completeness, but it has its limitations and restrictions. The great advantage of these electrical methods is that the heat applied to the tissues could be easily regulated, and increased or decreased at will and to suit individual requirements of

the case. Local application of heat over inflamed joints or inflamed pelvic appendages has resulted in marvellous cures and relief of unnecessary suffering. General rise of temperature of the whole body is accomplished by making the patient lie down within a cabinet (with only the head projecting out) and gradually raising the temperature of the cabinet. The patient's pulse and the rectal temperature are constantly observed. The temperature is maintained around 105 degrees F. for about 3 to 5 hours, depending upon the nature of the disease and the patient's ability to stand the strain of the treatment. The profuse perspiration that occurs during the treatment depletes the body of fluids and chlorides, and these are replenished by copious drinks of glucose water with common salt added. The treatment has to be repeated at suitable intervals and under efficient supervision. With proper selection of cases and with judicious combination of any other therapeutic measures that may be necessary, this method of treatment is an entirely safe procedure.

The indications for fever therapy are well known. Joint affections whether due to gonorrhoea or of the rheumatoid variety respond very well. Some nervous conditions such as cerebrospinal syphilis, disseminated sclerosis and chorea give very gratifying results. Genitourinary infections clear up quickly. Infective conditions of a generalised character are suitable for fever therapy. Most of the affections where one would think of non-specific protein therapy are best treated by electropyrexia, where there is the added advantage of being able to control the temperature as and when necessary. The rise of temperature helps to destroy the pathogenic organisms, stimulates the formation of antibodies, and effectively clears up the infection.

Used in suitable cases, fever therapy is a very useful method in the treatment of several diseases, particularly when clinical reports indicate uniformly good results in cases where other methods of treatment have failed to afford any appreciable relief to the patient.

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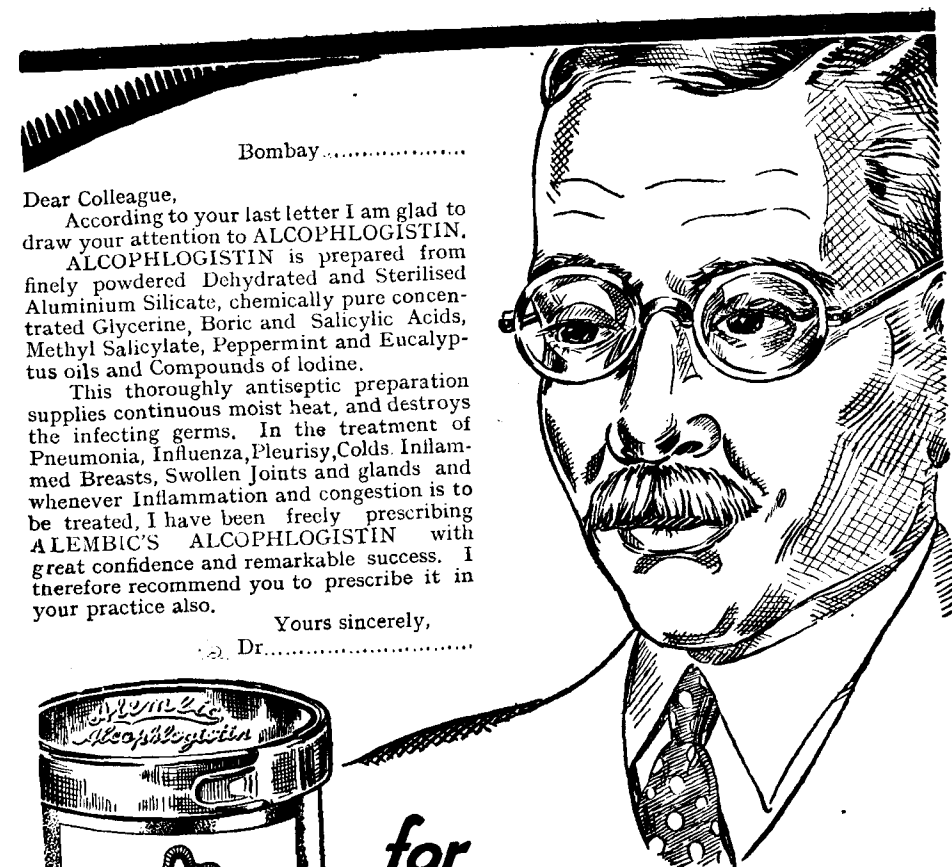
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## Extracts.

### THE USE OF PROGESTIN IN OBSTETRICAL COMPLICATION.

Frederick H. Falls discusses this in the *Illinois Medical Journal*, December, 1939.

Progesterone is the hormone extracted from the corpus luteum. It has an inhibiting action on uterine contractions and, when injected into suitable immature test animals (rabbits), it produces a progestational change in the endometrium.

#### EXPERIMENTAL OBSERVATIONS.

A rubber balloon was placed in the uterus of a woman 7 days post partum and the uterine contractions were recorded by means of a kymographic tracing. When pituitrin was injected the uterus promptly responded by developing rhythmic uterine contractions. When the injection of pituitrin was followed by an injection of one rabbit unit of progestin (oily extract), a prompt response in the form of inhibition of uterine contractions was noted. After the injection of progesterone, the uterus was refractory to further stimulation by pituitrin. The aqueous solutions were less prompt in producing inhibiting effect, but there is no reasonable doubt regarding their efficiency.

#### THREATENED AND HABITUAL ABORTION.

Most cases of threatened abortion, habitual abortion, or a combination of the two, may be successfully treated with progestin preparations. Obviously these preparations are valuable only in cases in which the foetus is alive. The presence of a dead foetus is suggested by Friedman test, the reaction of which is neither strongly positive nor negative. Complete, incomplete, and missed abortions are contraindications to treatment with progestin. There was no greater incidence of deformity in our treated cases that went on to maturity than in others not so treated.

#### PREMATURE DETACHMENT OF THE PLACENTA.

The cause of the detachment seems to be uterine contractions which are stimulated by the extravasation of blood between the placenta and the uterine wall. This is almost always a limited process at first and only becomes extensive after the uterine contractions have caused extensive separation. Since this is so, it would seem logical to apply progesterone by hypodermic injection in large doses as soon as the diagnosis of partial premature separation can be made from the early signs and symptoms. This we have been able to do in 5 cases with excellent results. The accident is especially apt to occur at about that period of gestation at which the foetus is on the border line of viability. By keeping the uterus from contracting and thus preventing further placenta separation, the foetus may

be given another three or four weeks of intra-uterine life. This will practically insure its survival if then delivered by caesarean section. Of course if the foetus is already close to term at the time of the first symptoms of premature separation and there is any evidence of foetal distress as evidenced by abnormalities of the heart tones, it should be delivered at once by caesarean section.

#### PLACENTA PRAEVIA.

In a given case presenting haemorrhage from placenta praevia in which a non-viable or very premature baby is present in utero, progestin should be given to decrease uterine contractions and thus inhibit further formation of the lower uterine segment and further separation and bleeding until the foetus has attained viability; even in cases in which the bleeding occurs late in pregnancy, progestin can be used to quiet uterine contractions pending arrangements for other forms of treatment.

#### PREMATURE RUPTURE OF THE MEMBRANES.

This is especially serious when it occurs before or just at the seventh lunar month, because of the danger of premature expulsion of the baby. In these cases we have used progestin preparation to prevent the onset of uterine contractions and have been successful in accomplishing this for varying periods of time from a few days up to a month. This has resulted in improving the chances of the baby to survive by reducing its prematurity. In these cases there is always a danger that the amniotic fluid will become infected from upward invasion of the vagina. When clinical evidence shows that this is taking place, the progestin injections are stopped and the uterus is allowed to empty itself, irrespective of the condition of the foetus.

The onset of premature labor has been controlled by the injection of progestin preparations. When labor has actually started, the effect of progestin on the frequency and strength of uterine contractions has been negligible.

The prophylactic use of these preparations is also recommended, for example, for a pregnant woman who is forced to take a long automobile trip or who receives a severe mental shock, and in various diseases associated with febrile reactions.

### EVALUATION OF SULPHANILAMIDE IN SUB-ACUTE BACTERIAL ENDOCARDITIS.

Wesely W. Spink and F. Hughes Crago report in *The Archives of Internal Medicine*, August, 1939, the results of sulphanilamide treatment of 12 patients suffering from sub-acute bacterial endocarditis.

The primary purpose in the study of these cases was to evaluate the effect of sulphanilamide on the clinical course of the disease.

Although the number of cases is small it appears that the drug had a definite beneficial effect on 2 of the 12 patients. Sulphanilamide was given orally, whenever possible, in daily divided doses totalling between 45 and 100 gr. (2.91 and 6.48 Gm.). As a precautionary measure against the development of acidosis, 5 to 15 gr. (0.32 to 0.97 Gm.) of sodium bicarbonate was given orally with each dose of sulphanilamide. We recovered organisms repeatedly from the blood of all 12 patients. The ætiologic agent was *Str. viridans* in 11 cases and *Staphylococcus albus* in 1.

There is little doubt that in some patients the administration of sulphanilamide will render the blood stream sterile, as determined by cultures of venous blood. This was true of 6 of the 12 patients in this series. However, this bactericidal effect appeared to be only temporary. It is likely that the organisms in the vegetations are protected from the action of sulphanilamide, even though the drug may have a bactericidal effect on those that reach the blood stream. It may be that certain strains of *Str. viridans* are more readily destroyed by sulphanilamide than others.

All of the 12 patients were febrile during their illness. In 4 there was a definite decline of the temperature, coincident with the administration of sulphanilamide. The temperature became normal or was only slightly elevated. In 5 patients the drug did not appear to affect either the temperature or the bacteraemia. In 1 patient, after sulphanilamide was given the temperature became and remained normal, but the bacteraemia was unaffected. In 2 patients, sulphanilamide therapy was accompanied by sterilization of the blood but was without effect on the temperature.

Although all the patients had some degree of anaemia during their illness, in only 1 could a rapid decline in the haemoglobin and erythrocyte levels be attributed to sulphanilamide. A majority of the patients had anorexia during the administration of sulphanilamide. This was so severe in some of the patients that the drug had to be discontinued. The patients also appeared listless and lethargic in varying degrees while taking the drug. It is of considerable interest that none of the patients exhibited more than a slight degree of cyanosis.

It appears from the foregoing observations that the administration of sulphanilamide to patients with subacute bacterial endocarditis will in some instances render the circulating blood free of organisms. However, we believe that sulphanilamide and its related compounds will be of doubtful value in the treatment of the disease itself because of the very nature of the focus of infection. The proliferating mass of bacteria situated well beneath the surface of the vegetation is probably protected, at least in part, from the action of free sulphanilamide in the blood as well as from specific anti-bodies. When the organisms approach the surface of the vegetation, they

are carried off in the circulating blood, and under these circumstances may be killed.

Since the presence of sulphanilamide in the blood may have a bacteriostatic effect on some strains of *Str. viridans*, sulphanilamide probably should be administered to any patient with valvular lesions who may be subjected to oral surgical procedures. It is well known that after the extraction of teeth or after a tonsillectomy a temporary bacteraemia caused by *Str. viridans* may result.

### THE IODINE TEST FOR CANCER OF THE CERVIX.

An editorial in *The Medical Times*, January, 1940, gathers together the history and various opinions on the value of this test.

In 1928 Lahm examined the material obtained by biopsy in twenty-five cases of disease of the cervix. He stained the sections of this material for the glycogen content of the cells, and in cases of cancer he found that the glycogen was decreased or absent from the protoplasm. He concluded that if one found a low glycogen content, or absence of glycogen in the cells of a biopsy specimen, he should be suspicious of the existence of a precancerous lesion, or at least be careful not to overlook cancer in a neighbouring portion of the section.

In 1928 Walter Schiller, in a paper entitled: "On Histological Early Diagnosis of *Portio* Carcinoma," pointed out that when one is examining biopsy material for the purpose of determining the glycogen content of the cells, it is proper to use an aqueous solution of formalin for fixing the tissue because the glycogen is in a modified form and not soluble in water.

In the same year Schiller published a long article on the same subject in which he said that the earliest appearance of cancer of the cervix reminded one of its similarity to leukoplakia and Bowen's disease of the skin: both are whitish, wrinkled spots. He was of the opinion that a curetting of such an area on the cervix would be better than an actual section with any cutting instrument. Again, he uses iodine-potassium iodide solution, such as is used in the staining of bacteria, which he applied macroscopically to diseased cervixes.

In 1929 Schiller published a fourth paper in which he advocated the application of compound iodine solution to cervixes which showed evidence of disease for the purpose of determining the areas from which biopsy specimens should be taken. He reported the results of the test in 126 cases of disease of the cervix. In this series 17.0 per cent. of the biopsy specimens showed that cancer was present.

In 1931 he made a further contribution, to the value of painting pathological cervixes with iodine solution for the purpose of diagnosing areas that might be carcinomatous.

In 1933 he says: "I discovered this method: vital staining with Lugol's solution. . . . When the normal cervix is painted with ordinary Lugol's solution (iodine, 1; potassium iodide, 2; water, 300) the epithelium acquires, in about half to one minute, a mahogany brown colour.

In 1934, he said that carcinomatous areas on the cervix are whitish, but not transparent. They resemble leukoplakia; but cannot be differentiated by clinical methods. With Lugol's solution, however, it is possible to visualize the smaller abnormalities so that they may be excised and submitted to the pathologist for diagnosis. The failure of the cancer cells to take the iodine stain depends on the absence of glycogen in their protoplasm.

Also, in 1934, in an eighth contribution, he says that the whitish or unstained areas should be removed with a small spoon curette, and that the final opinion of the malignancy of the lesion depends upon the result of the histologic study of the material thus obtained.

In 1936, he says that the best fixative solution is composed of absolute alcohol, 60.0; chloroform, 30.0; and glacial acetic acid, 10.0. In the series of cases reported in this communication, suspicious areas were found in 20.0 per cent. of the specimens. Of these only two proved to be cancer. He says: Even if only 1.0 per cent. of the women examined give a positive diagnosis, the result is still exceedingly satisfactory. For we must not forget that a carcinoma, when detected and treated in that early stage, gives nearly 100.0 per cent. security for definite, permanent healing."

In a paper published in 1937, continuing his development of the value of the iodine test, Schiller said that the test serves only to indicate suspicious spots. However, it should be applied to all cervixes as a routine. Between 1928 and 1937 he discovered 130 cases of early carcinoma of the cervix by its use. Up to 1931 he discovered fifty-one such cases. Of these forty-nine were alive and "perfectly well" at the time of writing (1937). One patient died of recurrence two and one-half years later and, on further histological study, another was found to have been farther advanced than was at first thought. In that paper Schiller says that the early carcinoma and the small one are not identical. He has proved to his own satisfaction that in the early stage carcinoma grows very slowly; later it grows so very rapidly. The "fact that carcinoma grows so very slowly at the beginning offers a marvellous chance for early diagnosis." "The initial phase lasts months, even two or three years or possibly longer."

After examining 3,000 so-called normal cervixes he has classified the lesions found into an ulcerative group, an invasive group,

and the carcinoma group which presents cytologic characteristics only.

In 1938 Schiller writes of the relation between leukoplakia, leukokeratosis, and carcinoma of the cervix. He says that leukoplakia is not a specific disease; it is a symptom that may be found in several abnormalities of the cervical mucosa. Long clinical experience has shown that the number of latent leukoplakias diagnosed with the aid of the iodine test far exceeds the number of those that are grossly visible. However, he is of the opinion that neither erosions nor inflammations form a basis for the development of carcinoma. He describes minutely the difference between the various degrees of cornification of the cells these variations parakeratosis, keratosis, and hyperkeratosis. He says: "Notwithstanding long follow-up studies of numerous cases, I have never as yet found areas of leukoparakeratosis or leukohyperkeratosis developing into carcinoma"; and again: "There is no casual relationship between parahyperkeratosis and carcinoma of the *portio*. From extensive material I could not find even one case of carcinoma that developed from a true keratosis."

In this paper by Schiller, the iodine solution suggested for carrying out the tests is referred to as compound iodine solution and Lugol's solution, but in the paper in which the formula is given, the material used is what we in the United States call Gram's solution. Lugol's solution is a much stronger iodine preparation, and is known as *Liquor Iodi Compositus*. The composition of this solution, according to the eleventh edition of the United States Pharmacopoeia, is iodine 5.0; potassium iodide, 10.0; distilled water, q.s. 100.0 (1936).

According to Graves the test described by Schiller is specific for the determination of the *absence* of cancer of the vaginal portion of the cervix and the vagina. He advocates the following technique: A thick swab of absorbent cotton and gauze is prepared on the end of a stout wooden applicator and dipped in Lugol's solution. This swab is then pressed firmly against the anterior lip of the cervix, exposed by a speculum or by retractors. In this way the upper vagina is flooded with the solution, which instantaneously stains the normal tissues, except the mucous membrane of the endocervix, almost black. Any area of the vaginal portion that does not take the stain must be regarded with suspicion. The suspicious area is then curetted with a specially sharpened spoon curette. The strip of epidermis thus secured is immediately placed in hardening solution and sent to the laboratory for histological study. He says "We are finding the Schiller test an indispensable aid in the search for early curable cancer. Failure of the stain indicates certain other abnormal conditions, two of which, leukoplakia and intense cervicitis, are potential precursors of cancer and require treatment." He recommends the test to the general practitioner for trial.

Frank and Healy recommend the Schiller iodine test for the detection of cancer of the cervix.

Galloway says that Schiller's test is a simple, painless procedure, requiring no expensive apparatus and consuming little time. It is primarily for office routine or for periodic examinations of patients who have no symptoms of cancer.

Henriksen considers the Schiller test valuable. He questions its specificity for the absence of cancer, however. He applies the iodine solution with an atomizer.

Meigs says that in approaching pelvic surgery Schiller's test is a necessary part of the physical examination.

Norris says that the iodine test of Schiller will indicate the suspicious areas from which to take biopsy specimens.

Novak is of the opinion that the chief value of the Schiller test lies in indicating the areas from which tissue for biopsy should be taken. And in this view of the value of the test Phaneuf agrees.

Baer says that Schiller's iodine test is devised to show tiny lesions of the cervix which might be early carcinoma and which should be promptly curable. In order to be effective the test must be employed as a routine and biopsy specimens should be obtained from all suspicious areas. When the microscopic picture is clear cut, the lesion is usually one which should have aroused suspicion without the employment of the test. Other specimens studied because they do not stain with iodine may show what Schiller calls the "preinvasive" stage of carcinoma. However, he considers the test "inadequate."

Martzloff says that in order to recognize cancer of the cervix, "there should be adequate exposure of the cervix, adequate illumination and deliberate, thoughtful inspection." He is of the opinion that the iodine test is not pathognomonic of cancer, "though it may possibly be a signal which calls for further study."

Some of the criticisms that have arisen concerning that test may be the result of misunderstanding about the solution to be used. It seems to us that the weaker solution of iodine, known as Gram's solution, is preferable to the stronger solution, known as Lugol's.

## Medical News and Notes.

### THE KRISHNA DISTRICT MEDICAL ASSOCIATION, MASULIPATAM.

(The Krishna District Branch of the Indian Medical Association.)

Minutes of the 15th monthly meeting held at Masulipatam on Saturday the 20th July 1940 :—Dr. K. Venugopal Rao Naidu, L.M. & S., in charge of Government Head Quarters' Hospital demonstrated several interesting cases in the Hospital and, the doctors in charge of the patients explained in detail practical points about diagnosis and treatment of the following cases :—

- (1) Aortic Aneurysm ; (2) Acute Leprosy ; (3) Hæmato Colpos simulating uterine fibroma ; (4) Vesicular Mole ; (5) Pelvic Abscess simulating Uterine Fibroma ; (6) Phosphatic deposits of stone in bladder removed by Lithotripsy ; (7) Huge Lipomata over and inside Deltoid and calf muscles ; (8) Case of Gastro-Enterostomy with Angiomata of Mesenteric Vessels in the Right Iliac Region ; (9) Two cases of Osteomyelitis.

The following were some of the resolutions unanimously passed :

- (1) A resolution was moved from the chair to place on record the appreciation of services rendered by Col. T. S. Shastry, I.M.S., to the Association.
- (2) Dr. K. Venugopal Rao Naidu L.M.S., Assistant District Medical Officer, incharge, Krishna, was unanimously elected President of the Association in the vacancy caused by the transfer of Lieut-Col. T. S. Shastry, I.M.S., (Military Duty, Jubbulpore).
- (3) Dr. K. S. Ray M.A., B.Sc., M.B., Ch.B., (EDIN.) was nominated as the President and Dr. D. S. Ramachandrarao, M.A., M.D., Bezvada, Dr. K. Krishnamurty, L.M.P., Chodavaram, and Dr. B. Tirumalrao, L.M.S., F.R.C.S. etc., Superintendent, King George Hospital, Vizagapatam, were nominated as Vice-Presidents to the All-India Medical Association.

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