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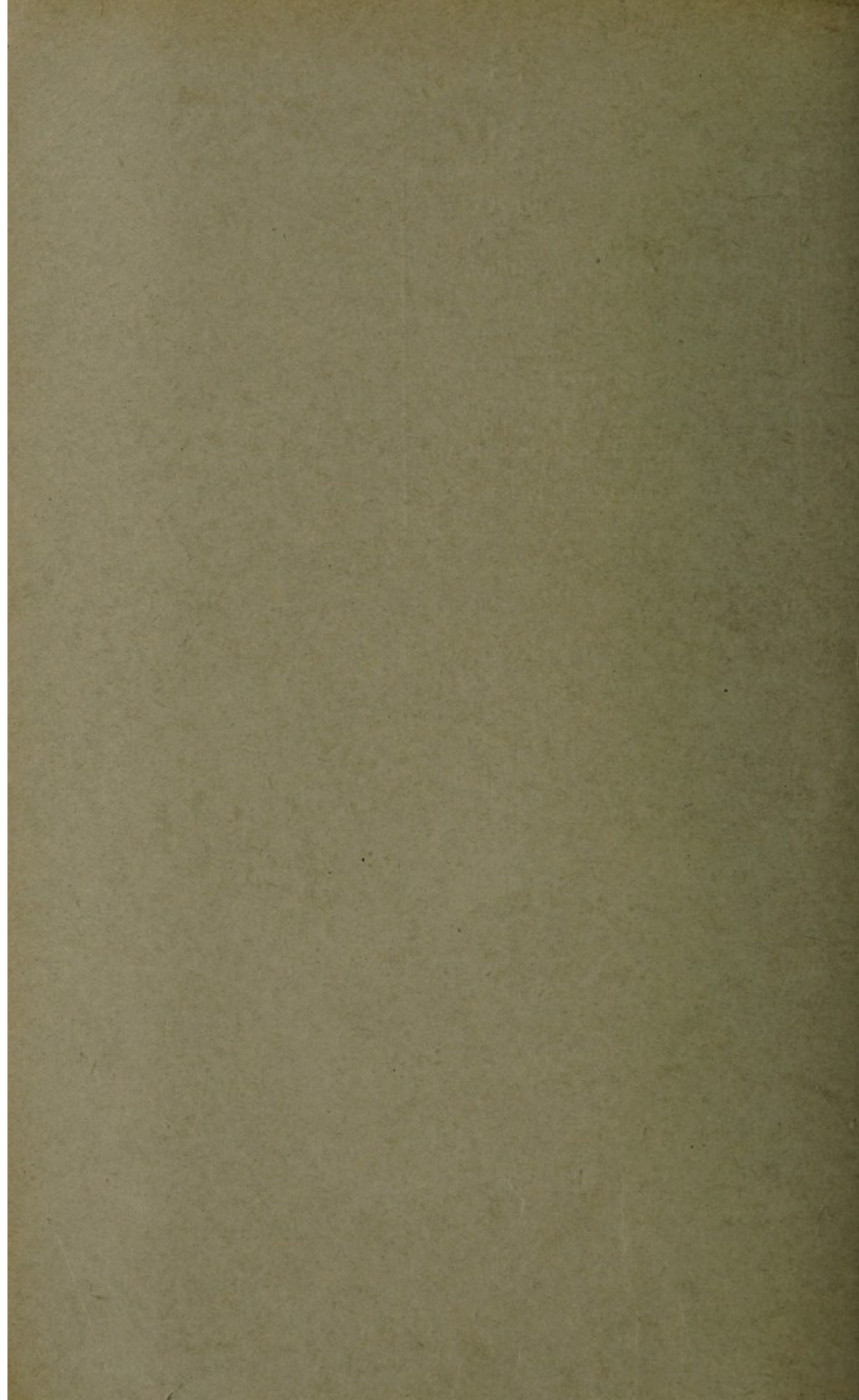
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WHAT IS THE BIOLOGIC FACTOR IN PRIMARY STERILITY?

BY WILLIAM SEAMAN BAINBRIDGE, Sc.D., M.D., C.M., NEW YORK CITY

STERILITY has practically always held a place of absorbing interest in medical literature, doubtless due, in part, to its relation to the State, as well as to the life of the individual. Since the enactment of the Mosaic law which stipulated that, after ten years of barrenness in his wife, a man was permitted to form a new alliance, sterility has been the subject of an infinite number of theses, both legal and medical. The Old Testament, for example, stresses the importance placed upon the fertility of woman in the story of Jacob who, while he loved Rachel better than Leah, put Rachel aside for her less attractive but more productive sister.

In ancient Rome, Spurius Carvilius was one of the first husbands to put his wife aside because of her sterility, and among the ancient Greeks, as among the Jews, barrenness was considered an affliction and a disgrace. As early an authority as Aristotle, in his essays, commented on sterility in woman and pointed out the fact that early marriages very probably were a basic cause of the sterile state. Kay quotes Pallas to the effect that the well-to-do Circassians gave a dowry to their daughters only after the daughters had proved themselves fruitful.

In spite of the fact that sterility, both primary and secondary, has always been a theme of intense interest to the essayist, from the time of Hippocrates, Celsus and Pliny, to the current medical writer, the etiologic factor which governs many cases of primary sterility has remained a great mystery and little more is known of it today than was known at the time when Moschion Diarthartes wrote his *Manual for Midwives* in the early days of the sixth century or when, many hundreds of years later, William Buchan (1816) published the dogmatic statement, that it is very certain that high living vitiates the humors, and prevents fecundity.

There can be no doubt of the frequency of the unproductive marriage, though most of the statistics regarding it vary to a degree where a reliable estimate is impossible and, of course, it is practically impossible to differentiate, statistically, between induced sterility and sterility resulting from a biologic or any other cause.

The following estimates of sterile marriages are those of dependable statisticians and, even so, the figures must be, at best, considered approximate. The statistics cover the broad aspects of sterility, without regard to the causative factor behind the condition.

Ansell estimates the number of sterile marriages as 8%; Simpson, as 10%; Duncan, as 15%; Stark, as 19%; Graham, as 20%.

NOTE: While we have encountered an allusion to a test of "the donor law" in relation to sterility, we have been unable to find any account of the cases typed, or the definite results of such typing.

Giles states "that for England it is a sound deduction that the sterile marriages may be estimated below 15 per cent." For France there is a general consensus of opinion that the ratio of sterile marriages is exceptionally high. There is no question but that the unproductive marriage in America is increasing, but as has been stated, to what extent this trend is due to birth control and to what extent to mechanical factors, or to a biologic influence would be mere guesswork to attempt to estimate.

While this particular paper is not concerned to any degree with sterility which is due to mechanical causes, it seems necessary briefly to review some of the most important of these mechanical factors in order clearly to distinguish between them and the type of sterility due entirely to a probable biologic influence. Apparently, unsurmountable difficulties, due to our ignorance of the pathogenesis of primary sterility, have always impeded our efforts to analyze the etiologic factor responsible for this condition, and it is because we hope that we may direct concentrated research towards the discovery of this unknown etiologic element that we venture to offer our hypothesis, today.

To recognize such obvious origins of sterility as absence, malformations or malpositions of the genital organs, in either mate, is not usually a difficult problem. Malchow states "that a certain small percentage of the cases in which the women are sterile may be due to congenital malformations." In the female there are some anatomic defects which may be directly responsible for the sterility, acute ante-flexion or retroflexion of the uterus; procidentia; stenosis of the vaginal canal; pin-hole os; rigidity of the hymen, etc. Many of these conditions can be remedied by surgical measures, enlarging the canal by dilatation; amputation of the cervix, or other type of corrective or plastic surgery of the adnexa. So eminent an authority as Block states that the congenital malformations giving rise to the sterile state are exceptionally rare. Male, as well as female anatomic abnormalities may, in many cases, be corrected by surgery and even for such apparently hopeless conditions of the male as azoospermia, certain of our prominent surgeons believe epididymovasostomy to be of value.

Infantilism of the uterus and ovaries is another anatomic condition which seems to have considerable bearing on sterility. Where there is reason to believe that the lack of fertility may be due to the under-development of these organs, mild irradiation may be carefully tried. Medical literature, however, cites numbers of cases where roentgen-ray treatment has caused the menses to cease and has, apparently, arrested the development and activities of the ovaries. Glandular therapy also is advocated by many of the endocrinologists, in connection with undersized ovaries and uterus, and reported successes from this

line of treatment are frequently encountered. Iscovesco, of Paris, whose work has been reviewed by Sajous, says that he has extracted from the corpus luteum, as well as from the entire ovary, a number of lipoid substances, one of which, a yellowish, waxlike body, soluble in oil, was found to exert a pronounced stimulating action upon the genital system—injections in young female rabbits causing a striking enlargement of the ovaries and uterus to several times the size noted in the control animals. While organotherapy is, apparently, of use in some of these cases of infantilism, transplantation of ovarian glands has secured results far beyond the point produced by the use of oral glandular therapy. In this connection Biedl says, "The medical method is in reality a substitute for the surgical and is a less perfect and less certain imitation of natural measures. Where the extract is employed, only that portion of the active substances which is, for the time being, in the tissues and this is doubtless very small, becomes absorbed—while after transplantation the increase is incalculable because there is constant production." From the foregoing evidence, it seems a fair assumption that in cases of undersized ovaries and infantile uterus, growth of these organs sometimes may be stimulated by the use of mild doses of roentgen ray, or by organotherapy. Transplantation of ovarian tissue, however, seems a far more certain method of stimulating growth and activity.

Complete or even partial frigidity is another of the factors which many writers claim may affect sterility. Medical opinion varies to a very great extent in regard to the relation between frigidity and unproductiveness. Kisch states "that he considers sexual excitement, by its reflex influence on the cervix and cervical secretions, renders the passage of the spermatozoa easier." Other writers of equal weight claim that there can be no connection between frigidity and sterility, inasmuch as many women who acknowledge partial or even total frigidity produce offspring.

While the congenital and idiopathic types of sterile patients are not so numerous as to prove a serious menace to the total birth rate, there is no question but that a high percentage of sterility originates in acquired conditions. Sterility as a result of sepsis; endocervicitis; endometritis; degenerations; tumors, especially the small cysts and fibroids which may block the uterine passage; occlusion of the tubes, and constitutional disease is an extensively prevailing condition. Some of these types can be benefited by simple surgical measures, a curettage; removal of the fibroids, etc. Sterility as the result of venereal disease is of very frequent occurrence. Graves considers "that of all causes of sterility, gonorrhea is by far the most important, because of the blighting effect of the disease on the procreative powers of the man as well as the woman." Lier and Ascher found that "70 per cent of sterility in man is due to gonorrheal infection." In comparing the relative re-

sponsibility of man and woman in sterile marriages, they estimated that of man at about 40 per cent and that of woman at about 60 per cent. Fortunately, with our present-day tests, venereal disease, as an underlying element of sterility, can usually be diagnosed. To eliminate the condition, after it has been properly diagnosed, is a more difficult problem. To remove the great masses of syphilitic or gonorrheal adhesions from the pelvis and restore to normal what our distinguished Fellow terms "a gummed-up pelvis" is a task of no mean dimensions.

In reviewing the most obvious factors of acquired sterility, we must, of course, speak of the pathologic cervical and vaginal secretions. Reynolds lays much stress on the pathology of these secretions in relation to sterility. He says "that the vaginal hostility is mainly enzymatic and of bacterial origin. Cervical hostility is mainly mechanical and of inflammatory origin. Either or both of these secretions may and frequently do present conditions which absolutely prevent fertility through their destruction of the spermatozoa and which are yet so far external to the physiology of the woman as to excite no ill health, to produce no symptoms other than the persistent sterility." Medical measures which will bring about alterations of these pathologic secretions must be guided by the type of microorganism the microscope reveals and the acid content of the discharge.

The endocrinologic factor in sterility may be of as much importance as many of our medical contemporaries consider it, but we must reason that in a woman who menstruates normally and in whom the tubes and ovaries seem properly developed, ripe ova are probably given off at intervals and this must also apply even in cases of obesity. In these cases where menstruation is regular and the organs of normal development, the endocrinologic factor is probably of extremely minor importance.

Extreme anemia, or other constitutional disease, or cases of evident undernourishment should certainly be investigated when sterility is present. Diet influences the fertility of rats, and cattle conceive best while pastured in the richest grazing lands. I have not been able to find any well authenticated case of human sterility in which fertility has been favorably influenced through diet.

"Fecundation implies the union of normal spermatozoa with healthy ripe ova and the migration of the ova through the tube." Sterility may be due to the absence of either one or both of these factors or to the prevention of their union by obstruction, or by the blocking off of the fertilized ovum through the tube. Today, there are two scientific short cuts to determine whether the sterility is due to a recognizable cause, and one of the tests covers the possibility of the sterility of the male as well as that of the female. I refer, as is evident, to the Hühner test for sterility, and the Rubin test for the nonoperative determination of the patency of the fallopian tubes. The importance

of Rubin's method of intrauterine carbon dioxide inflation, when an artificial pneumoperitoneum is produced and the patency of the genital canal from the external end to the internal abdominal end is proved, is obvious. Of course we realize that this result can be secured if but one tube is patent and the other closed, as well as when both tubes are patent, but, as Dr. Rubin states "for practical purposes in the consideration of sterility, it suffices if one fallopian tube is patent."

The confusion and uncertainty attendant upon analyzing the various types of sterility have seemed almost unsurmountable—and to be able to eliminate the majority of the possible causative factors in a case of sterility by such a simple process as the "Hühner test" is indeed an achievement in applied research. To an audience of this type to elaborate the theory itself is unnecessary. Dr. Hühner makes a microscopic examination of the spermatozoa taken from the cervix practically immediately after coitus. As a result of this examination, made at this time, and the examination of a condom specimen from the husband, in cases where the spermatozoa obtained from the cervix are of doubtful character, the diagnostician is able to eliminate many of such causative factors of the sterility as those often emphasized by the medical writer, lack of orgasm in the woman; stricture of the urethra; epispadias; hypospadias and other conditions in the male; also the hyperacidity of the female (vaginal) secretions.

Having briefly reviewed the possible main causes in the problem of congenital and acquired sterility, we arrive at that type of sterility with which we are all familiar—the women in whom there is, apparently, no cause for the condition. The organism is sound; the tubes are patent; the male is normal. Every known method to influence ovulation has been tried—organotherapy; stimulation of the ovaries by roentgen rays, etc., but without result. To what is this lack of fertility due?

Biology recognizes a sex incompatibility,—a "selective sterility." On what is this biologic affinity, or antagonism based?

According to the early research relating to hematology, Landsteiner and Hektoen divided all human blood into four groups, as follows:

Group 1: Here the corpuscles are not agglutinated by any human serum, whereas the serums agglutinate the corpuscles of the other groups. This group includes about 50 per cent of all persons.

Group 2: In this group the corpuscles are agglutinated by the serums of other groups, whereas the serums agglutinate the corpuscles of Group 3 but not of Group 1.

Group 3: The corpuscles are agglutinated by all other serums, and the serums agglutinate the corpuscles of Group 2 but not of Group 1.

Group 4: The corpuscles are agglutinated by all other groups, but the serums are unable to agglutinate any human corpuscles. These are quite rare.

During the war Crile demonstrated that skin transplantation seems to take along blood-law lines. In the four blood groups: one will take all; four will give all; two will take two and four; three will take three and four.

Recent research in England seems to indicate that predisposition or resistance of tissue to malignancy is based largely on the blood group to which the individual belongs.

In the transplantation of glands, Tuffier of France, has established that homogeneous glands (glands transplanted between a recipient and donor of common ancestry) will thrive and function in practically every case, whereas a transplantation between a donor and a recipient in which there is no blood relationship is more apt to degenerate or disappear. The majority of Tuffier's experiments have been with the transplantation of ovarian tissue.

Research along the lines of the mendelian theory has indicated that certain strains show an inheritable infertility towards other strains. Remating of such strains will frequently evidence fertility on the part of both mates. Several famous cases in history bear evidence of the likelihood of such a possibility; a notable case was that of Napoleon and Josephine. Mated they were sterile but each remated proved a fertile partner.

Basing our hypothesis, therefore, on the fact that skin, tissue and gland transplantation seem to take along blood-law lines, we assume that "selective sterility," i.e., primary sterility uncomplicated by congenital or acquired conditions, may be due to a lack of affinity between certain of the blood groups, or to an immunity to fertilization produced by a combination of two blood groups. Evidence possibly contrary to this hypothesis is suggested by Golberts who makes the claim that consanguinous marriages are less fertile than nonconsanguinous marriages. However, verification of this theory is inadequate. Consanguinous marriage (marriage between mates of common ancestry) would place such mates, frequently, in the same blood group. The inference is that these mated couples are less fertile than those of diverse blood groups. However, genealogy vouches for the fact that many of the crowned heads of Europe have a common ancestry and apparently, these kings and queens are not less productive than their uncrowned and less closely related subjects. Also among the mountaineers of Kentucky, Tennessee and the Carolinas intermarriage is the rule rather than the exception and these mountaineer families are notably prolific. The offspring of such interrelated mates may not always prove of the highest order, mentally and physically, but at least they are not lacking in numbers.

Our most promising line of research in relation to primary sterility is concentrated study along blood-law lines.

H. Hirschfeld and others have demonstrated that the percentages of the four blood groups vary in the different races. Among the North Europeans Group 2 is predominant over Group 3, while the opposite ratio holds for Asiatics and Africans. Is there any connection between the productiveness of these races and the predominance of the blood group of the race?

(1) Since there is an apparent relation between the development of malignant tissue and the blood groups, why not a possible interdependence between the development of embryogenic tissue and the blood groups?

(2) May it not be possible that a blood group which evidences an immunity to malignancy, may for like reasons also evidence an immunity to fertilization?

(3) Is it not reasonable to deduct that a natural law which, apparently, influences the growth and functioning of transplanted skin and glandular tissue, may also influence the growth of embryogenic tissue?

Finally, what causes an immunity to fertilization can only be determined by continuous and unceasing biologic research and to stimulate such research is the basic aim of the paper presented here today.

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