Alumni Day - Talk - P+S
Apr 22 1960

GENETICS AND ANESTHESIA

At about the time when Dr. Ralph Waters was giving his first anesthesias in Sioux City, Iowa, there was published a description of human chromosomes, numbering 48, which was accepted as gospel truth for many years... and speaking of gospels, the Bible again serves as a source book, not only for anesthesia (And God caused a deep sleep to fall upon Adam) and resuscitation (Elisha stretched himself upon the child, his eyes upon his eyes, his hands upon his hands, his mouth upon his mouth.. etc.) but also for genetics. In the book of Genesis, Gen chap 30, Jacob selected spotted sheep from the flock and kept them for himself while giving away the others to his neighbors. In the Book of Revelations, Chapter 1, verse 14, "one like unto the Son of man" is described as "having head and hairs white like wool, as white as snow, and his eyes were as a flame of fire." Noah also was similarly described as an albino in one of the books of the Pseudoepigrapha.

Both genetics and anesthesiology have made tremendous strides in the last 35 years. These seemingly unrelated fields have had their paths cross at least once, and probably will meet many more times. A major advance in human genetics occurred only 5 years ago when a ~~Spaniard~~ Javanese and a Swede were unable to find 48 chromosomes in human cells. Others before them had had difficulty in finding all 48 chromosomes, but had laid aside their work, blaming the results on technical difficulties. Tjio and Levan, in January, 1956, published a short note in the journal HEREDITAS that the correct number of human chromosomes was 46. This statement has been verified in every chromosome counting laboratory in the world. How long it will be before recognition of this fact reaches standard medical textbooks is unknown. The 1959 edition of Nelson's PEDIATRICS still quotes 48. Another major advance came in 1944 when Avery, Macleod and McCarthy at the Rockefeller Institute identified DNA as carrying the heritable traits in bacteria. Brilliant work has been done here at the

Medical Center by at least three groups to add knowledge in this field... the demonstration of transformation of Hemophilus influenza bacillus by Hattie Alexander and her team, the chemistry of nucleic acids by Chargraff and Zamenhof, and the structure of viruses, by Harry Rose's group, Councilman Morgan, Calderon Howe, Dan Moore, and others. The gap between the biological terms chromosomes, genes, mutation and the chemical structure of nucleic acids, and the arrangement of its nucleotides is steadily closing.

One of the fields which is especially popular today is that of "inborn errors of metabolism" and here it is that anesthesiology becomes implicated. Although it is not definitely proven that there is a "one-gene, one-enzyme" relationship or that it is entirely specific, advances in this area occur almost monthly. A gene is now not an entity, but made up of gene particles, which are probably parts of the nucleic acid molecule. The relation of heredity to environment is being explored directly by transplantation technics of many kinds...mammalian eggs are transplanted shortly after fertilization into the uterus of a foster mother of the same species, the nucleus of one cell can be isolated and transplanted into another cell, and now even the chromosomes can be transplanted from one nucleus to another nucleus. In time, gene transplantation will be a possibility.

Most of you know what a dim view I take of explaining anesthesia complications by ~~pulling~~ putting forth the explanation of "sensitivity" of the patient... a glorious waste-basket for clinical carelessness. Obviously, there is a wide range of variability in the threshold of patients to all the drugs we use. It is up to the clinical anesthesiologist to predict where his particular patient fits into that range with each drug, ~~and~~ to be prepared to admit his judgement wrong when the patient surprises him by some unexpected reaction, and to correct his error immediately. The unexpectedly long recovery from the use of even moderate doses of

succinyl choline is one of these reactions. In 1956, Lehmann and Ryan suggested an inherited difference in serum cholinesterase and, more recently, Kalow in Canada has found such a family. The important point is to pick up carriers of this gene whether in single (heterozygous) or double (homozygous) dose before using succinyl choline.

Until recently, such predictions of gene frequency have rested on a mathematical model. The names of Hardy, an English mathematician, and Weinberg, a German physician will stir your genetic subconscious minds. In 1908 they combined their ideas on gene or allele frequency in populations with completely random matings, and provided the formula which still remains remarkably accurate. Let us use albinism as an example only because no gene frequency relating to enzymes concerned with drugs used in anesthesia has been well worked out. Albinism is due to the double presence of the undesirable, recessive gene, d. which corresponds to q. in the H-W formula: $p^2 + 2pq + q^2 = 1.0$ (100%). The frequency of albinism is about 1 in 20,000, which corresponds to q^2 or one frequency of dd. Thus, q = 1/141. Since p, or the presence of the gene preventing albinism, is equal to 1 - q, p = 140/141, which for practical purposes equals 1. The carriers or the heterozygotes, are equal to 2pq, here2x1x1/141 = 1/70. The very great rarity of albinism does Not mean the great rarity of carriers. Almost 1.5% of us carry one gene for albinism. There are 287 x as many carriers as have the condition. The formula pertains well to the existance of the many blood groups, the tasting of phenylthiocarbamide, and many other situations.

Fortunately, there are appearing more and more chemical ways of determining the presence of heterozygotes. One of these is the chemical assay of the enzyme in

question from the blood stream. In galactosemia, Hsia in Chicago is able to pick out carriers of the gene for galactosemia by analysing for the amount of galactose-1 phosphate-uridyl transferase in the serum. There are significant differences in the amount of the enzyme for those with the disease, those carrying one gene, and those with no such gene.

A similar technic has been described for the presence of serum cholinesterase, though the method has not been confirmed elsewhere. The chemical agent used to test the activity of the enzyme, by inhibiting it, is none other than dibucaine, (our old friend, Nupercaine). Under standard conditions, dibucaine produces about 79% inhibition of cholinesterase activity in normal individuals, and in succinyl choline sensitive individuals, only about 16% inhibition was obtained. The dibucaine number, DN, refers to the percentage inhibition. The low DN number in sensitive individuals is thought to be part of an atypical pattern of substrate specificity and inhibition characteristics, and that such individuals synthesize an enzyme protein different from the usual one, not just a smaller amount of normal cholinesterase.

Kalow and Staron have examined a Canadian population and found that the curve of DN values is trimodal, with values of 79 for those without the undesirable gene, 16 for those who are homozygous with a double dose of the gene, and are sensitive to succinyl choline effects, and about 62 for those who are carriers and heterozygous. The frequency of this gene in the population they examined is about 0.014, or similar to the situation with albinism described above.

Apparently the three genotypes are determined genetically. Here is an example of one family tree of four generations showing the occurrence of sensitivity to succinyl choline. Seven such families have been studied. Kalow feels that it is

imperative for affected individuals to carry cards with them, warning physicians of their unusual sensitivity, and that it is the physician's duty to investigate all members of the family. A similar type of enzyme deficiency may well occur to interfere with the degredation and excretion of many other parenteral drugs commonly used by anesthesiologists. The sooner methods are devised to identify abnormal enzymes, or inadequate quantities of normal enzymes, the safer will be both the patient and the physician.