Vol. XLII JUNE 1963 No. 6

The NOVA SCOTIA MEDICAL BULLETIN

Editorial

Chronic Illness and Medical Care

In recent years there has been a progressive increase in the number of patients suffering from some chronic disease, either congenital or acquired in nature. In the past many patients were unable to be treated during the acute phase of their illness and succumbed to the primary condition or to some complication frequently bacterial in origin. Today the recognition of many new diseases, the introduction of new drugs and equipment and the development of new surgical techniques has resulted in an increased number of patients surviving in reasonably good health, but with some limitation in physical or mental well being.

One may consider for a moment if the best medical care is being provided to such patients .

The busy practitioner, visited repeatedly by a sufferer from some chronic illness such as osteoarthritis, mental retardation, poorly controlled diabetes mellitus, chronic cardiac disease, sequelae of a cerebro-vascular accident, carcinoma or recurrent skin disease, and who has not responded to recommendations of a consultant may feel uncomfortable, insecure and frustrated in not being able to help his patient.

He may find the course of the disease and the situation unfamiliar to him. Unable to offer any rapid cure or lengthy assistance and frustrated by being placed in a position that he has not been trained for, he may try to ignore the patient, or become short tempered and unintentionally cause great anxiety and extra worry.

Not uncommonly the training of the young medical student has been directed primarily toward the treatment of acute illness with no attempt made to have him understand the problems and natural course of many chronic diseases. He may be unexposed to the frustrating situation of seeing a patient who is chronically ill, with no specific medication of benefit except the kind words and understanding of a family physician and friend.

Greater education of the medical student regarding the problem of chronic illness and the chronically handicapped would seem desirable. The use of chronic convalescent hospitals and nursing homes for teaching have assisted greatly in the understanding of such problems, both regarding the disease process itself and education in the techniques of handling chronically ill patients.

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He should also be educated regarding visitation and responsibilities to such patients in chronic institutions.

Last year an editorial in the Canadian Medical Association Journal criticized physicians in charge of out-patient clinics for not referring patients back to their family physician. In many cases this criticism is justified. However, the article failed to discuss one important aspect of why some patients should continue to attend a special out-patient clinic.

The incidence of certain chronic diseases is relatively low and they may be seen infrequently by the family physician, who is therefore unable to become familiar with the particular problem. However, the continued well being and the actual survival of some chronically ill patients depends on a sound knowledge of a particular disease and a close familiarity with its problems. It is in such cases that a physician seeing thirty or forty patients with a particular disorder at regular intervals and aided by well trained medical and para medical personnel may well provide greater benefit to the patient than the family physician alone.

In children the length of survival of patients with either diabetes mellitus or congenital heart disease is directly dependent on close observation and frequent education of the family and the child by a highly experienced physician. In such cases the family physician continues as a most important part of such a programme acting as the peripheral member of the team, while the clinic physician, nurse and para medical personnel are the central members, all working together to provide the best and most effective medical care programme for those chronically ill patients.

Such a programme exists in Nova Scotia in many areas, but requires increased effort on the part of the medical school, the medical clinics and practising physicians if it is to flourish and grow.

W.A.C.

From the Bulletin of 40 Years Ago

The Medical Society of Nova Scotia Bulletin, May, 1923.

At the last meeting of the Provincial Medical Board, a communication from Dr. G. C. W. Bliss, of Amherst, relative to quack treatment of cancer, led to a general discussion on the subject. During the "cancer week" in November last, Dr. Bliss wrote a strong letter to the Amherst press in which he cited instances in which resort to quackery had led to delay in applying for surgical treatment until there was no hope for cure or even relief. The Board is giving consideration to the possibilities of success in bringing action against all unlicensed persons who practice medicine, and expects shortly to be in a position to make an interesting announcement in this particular. Meantime it asks that reference be made in the "Bulletin" to the great desirability of associates with quackery.

The Anti-Cigarette Campaign
A Wholehearted Effort?

by
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The President of the Canadian Medical Association, Dr. M. R. McCharles, in a letter appearing in the Canadian Medical Journal, March 16th, 1963, urged each member of the Canadian Medical Association to support educational activities aimed at reducing cigarette smoking, especially those educational activities of the Canadian Cancer Society; asked the medical profession to smoke instead pipes or cigars; and asked that if the individual doctor continues to smoke cigarettes that he refrain from doing so in the exercise of his professional duties. This latter recommendation was made because of the influence of the doctors on children and young adults, and as he said, "few in our society whether members of the medical profession or not, whether smokers or non-smokers, would wish to see this dangerous habit passed on to the next generation."

It would seem that some physicians are not convinced of the epidemiological evidence on which the association between cigarette smoking and lung cancer is based. The cornerstone of all such statistics is still the study by Richard Doll and Bradford Hill published in the British Medical Journal in 1950, in which they compared the smoking habits of 709 people with lung cancer to 709 people of similar age and sex with disease other than lung cancer. Only 2 out of the 649 male patients with lung cancer were non-smokers. 27 of the 649 patients without lung cancer were non-smokers which is statistically highly significant.

Critics of Doll and Hill's original paper have mainly contributed further evidence to show that there is a link between smoking and cancer. Thus, Dr. R. D. Massey showed that the number of cigarettes smoked per day made little difference to the age of onset of lung cancer, as did the age of starting to smoke. He wondered why heavy smokers were not stricken with the disease any earlier than light smokers although the incidence of disease is greatest in heavy smokers. He concluded that if there was a carcinogen in tobacco it did not act in the same way as other known carcinogens where the incidence of disease is related to the duration of exposure of the carcinogen. From this criticism it was discovered that cancer of the lung occurs in nickel mines, cobalt mines, coal mines and such in the same relationship as smoking—there is no relation to the length of time worked in the mine.

In their second report in 1956 Doll and Hill showed that the death rate from lung cancer of smokers and non-smokers was in the ratio of 90 to 7 while the death rate from other cancer, coronary disease and other causes was remarkably similar in smokers and non-smokers. Death from respiratory disease was, however, much higher in smokers than non-smokers. Also Doll and Hill showed, to the satisfaction of themselves and other statisticians at least, that giving up smoking cigarettes was worthwhile so far as lowering the chance of getting lung cancer was concerned. Other workers such as Hammond and Horn, Dorn, Dunn et al, have shown that smokers have an average mortality from lung cancer at least seven times higher than non-smokers, the mortality ratio increasing rapidly as more than ten cigarettes a day are smoked.

Perhaps the severest critics of the association between lung cancer and smoking are R. A. Fisher of England and Dr. B. Birksen of the Mayo Clinic. These people are statisticians. Their main bone of contention - that there

has been a failure to reproduce tumors from smoking cigarettes in animals - has lately been overcome. Their suggestion that there may be a constitutional difference between non-smokers and smokers is valid only if one supposes that such a change in constitutionality has occurred in the last two decades. Birksen's statement that it is "popular" to diagnose cancer of the lung will hardly be acceptable to the practicing doctor. Nevertheless, Fisher has gone on record as stating that "while the relationship between cigarette smoking and lung cancer is not established, it is logical to give up the habit until the association is either proved or disproved." Incidentally, Doll and Hill in their 1956 publication in the British Medical Journal also showed that the death rate amongst pipe smokers from cancer of the lung was about one quarter the death rate of those who smoked only cigarettes and about half the death rate of those who smoked pipes, cigars and cigarettes.

In 1961 there were 2500 deaths from cancer of the lung in Canada. About 20% of all cancer deaths in North America are due to lung cancer, and the death rate from lung cancer in those who smoke more than 20 cigarettes a day, is 50 times that of a non-smoker. Deaths from bronchitis and emphysema in heavy smokers may be as much as six times that of non-smokers and deaths due to coronary disease is doubled in heavy smokers between 50 and 70 years of age. The incidence of cough and sputum (with or without bronchitic illness) in cigarette smokers in general is said to be 25 times that of non-smokers. Since the air in cities contains benzpyrene and other carcinogenic hydrocarbons, and since a man breathes 30 lbs of air a day, it follows that the highest incidence of carcinoma of the lung should occur in cigarette-smoking taxi drivers who live and operate in downtown Los Angeles - and this may yet be proved to be so.

Treatment of cancer of the lung by the best available methods today yields a five year survival result of 5% to 8%. Possibly the mortality would not change much if no treatment were offered at all. A recent experience in Halifax shows the futility of trying to diagnose early lung cancer by pap smear. A patient who had a positive pap smear did not develop his carcinoma of the bronchus for 2 years following the original cytological diagnosis, and when it was discovered clinically it was already inoperable.

Obviously any method of prevention of the disease is to be seized upon if the mortality is to be lessened. It seems not unreasonable to urge people to quit smoking until a safer cigarette is made, or better methods of treatment become available. Certainly we have a debt to the new generation to make them understand the implications of beginning a habit which has the marks of true addiction.

It will be said that the effort needed to materially reduce the incidence of cigarette smoking is too great, and that since the Federal Government would lose about $365,000,000.00 a year excise tax at present rates should cigarette smoking be rapidly discarded, Government support might be lacking. This however has not been the case in several European Countries.

The advertising budget of cigarette companies is large, and as Mr. E. S. Hallman, Vice-President in charge of Programming, Canadian Broadcasting Corporation said before a meeting of the Central Cancer Committee of the C.M.A. recently, their policy in its effect to prevent mass acceptance of the dangers of cigarette smoking is very clever and most successful. There is little doubt that cigarette advertising is false and misleading. In the U.S.A. it has been false and misleading to the point where F.C.C. regulations have recently been promulgated restricting the advertising content of copy put out by the cigarette companies. While it seems hopeless to ensure that all advertising

media will not contain false and misleading cigarette advertising, it may be that corporate bodies associated with specific media, such as the Canadian Broadcasting Company, would have a conscience and might be accessible to pleas that cigarette advertising be restricted. This, in fact, has happened in England where cigarette advertising is not allowed before 9:00 p.m. in the evening, and the advertising copy, I believe, is restricted so that no reference is made to pleasure, sophistication, manliness, etc. That Mr. Hallman's judgment of the cigarette companies' public relations effort was only too accurate, was borne out by an incident which happened recently in Toronto. The President of the C.M.A., Dr. McCharles, had made a short statement for C.B.C. to the effect that the link between cigarette smoking and lung cancer was too strong to be any longer ignored and that the Cancer Committee was meeting to advise the general meeting of the C.M.A. on a campaign to lower the incidence of the disease. This statement was taped at approximately 6:30 p.m. and appeared in the 11:00 o'clock news that evening. Yet, immediately following Dr. McCharles on the C.B.C. News there appeared the image of a spokesman for the tobacco companies - obviously a **Scientist,** in a white coat with the collar turned up - who said that, of course definite proof was still lacking that cigarette smoking caused cancer, and other evidence may yet be turned up to reverse this opinion. The statement was bland and "sincere" - it effectively nullified Dr. McCharles' statement.

The annual meeting of the Canadian Medical Association in Toronto in June of this year will be looked forward to with great interest by all those who have any interest in the cigarette problem. The medical profession has declared that it is taking the field against the habit of cigarette smoking. It is hoped that each and every physician will lend his support to the campaign presently being conducted by the Canadian Cancer Society, or any of the anti-cigarette societies, such as the Non-Smokers Association of Canada. Our children must be warned - some would say protected - from the dangers of cigarette smoking. Surely those that wish to smoke can satisfy their craving with pipe or cigar.

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Role of Tobacco Smoking in Causation of Chronic Respiratory Disease*

Study undertaken in population group in Berlin, New Hampshire, revealed significant link between cigarette smoking and chronic respiratory diseases. Risk of disease doubled after 3000 packs of cigarettes had been smoked, the equivalent of one pack a day for eight years.

In a study of chronic respiratory disease undertaken in Berlin, New Hampshire, in 1961, the prevalence of various forms of respiratory disease according to age, sex, current tobacco smoking habits, and lifetime cigarette consumption was determined. A questionnaire supplemented simple tests of pulmonary ventilation in a probability sample of residents 25 to 74 years of age.

Subjects were assigned to one of the following categories; never smoked cigarettes; former smoker of cigarettes; and currently smoking 1 to 10, 11 to 20, 21 to 30, 31 to 40, or 40 or more cigarettes a day.

The approximate number of packages of cigarettes smoked during a lifetime was estimated from the age the subject began regular cigarette smoking.

Disease Classification

The disease categories were defined as *chronic bronchitis*, if a subject produced phlegm on at least four days a week for three months of a year for three years; *asthma*, if a subject had a history of bronchial asthma and it was still present (because asthma was usually associated with one of the other diseases, it was not analyzed separately); *irreversible obstructive lung disease*, if a subject had a history of wheezing or whistling in the chest and dyspnea not due to known causes; and *all chronic respiratory disease*, including all subjects who had at least one of the diseases listed above.

There was a regular increase in the prevalence of chronic bronchitis with age in men, ranging from 24.1 per cent in the age group 25-34, to 34.7 per cent in those 65-74. The age gradient in irreversible obstructive lung disease was irregular for both men and women.

The prevalence of chronic respiratory disease in men consistently exceeded that in women for each age group except that from 25 to 44; women in this age group had a slightly higher prevalence of irreversible obstructive lung disease. Irreversible obstructive lung disease appears to be more frequently combined with chronic bronchitis in men than in women. In women the latter may remain a pure disease, with little sputum.

Of the 532 men interviewed, 261, or 49.1 per cent, were currently smoking cigarettes, and 200, or 32.9 per cent, of 607 women were cigarette smokers.

Increased Smoking - Rise in RD

There was almost uniform progression in the prevalence of all chronic respiratory disease, chronic bronchitis, and irreversible obstructive lung disease with increasing cigarette smoking. Among men, the rate for all chronic respiratory disease rose from 19.7 per cent among those who had never smoked cigarettes to 87.7 per cent among those who smoked more than two packs a day. Among women, it rose from 17.2 per cent among nonsmokers to an average of 43.3 per cent among all those who smoked more than a pack a day.

*Reprinted from the Abstracts of the National Tuberculosis Association, March 1963.

The comparable rates for chronic bronchitis in relation to the number of cigarettes smoked were, for men, from 15 per cent among non-smokers to 75.3 per cent among those who smoked more than two packs a day, and, for women, from 9.4 per cent (nonsmokers and ex-smokers) to an average of 27.3 per cent of those who smoked more than a pack a day.

Chronic respiratory disease in smokers increased above that of nonsmokers only when a threshold of 3,000 packages had been passed, or the equivalent of one package a day for about eight years.

Despite age standardization, the risk of disease doubled after 3,000 packs had been smoked, and more than tripled after 18,000 packs. However, after standardization to lifetime cigarette exposure, age was found to be no longer significantly associated with the presence of any disease in men; a *significant* association with age remained for irreversible obstructive lung disease in women.

Lifetime Smoking Signified

Since the lifetime cigarette-smoking exposure was a function of age, current and past smoking habits and the age smoking began, it could logically be regarded as a composite of several variables. In men, however, after standardization to lifetime exposure, current cigarette smoking was still found to be *significantly* associated with the presence of chronic bronchitis but no longer with the presence of irreversible obstructive lung disease. After standardization to current cigarette-smoking habits, however, lifetime cigarette-smoking exposure was still found to be *significantly* associated with the presence of chronic bronchitis and *highly significantly* associated with the presence of irreversible obstructive lung disease. In women, however, standardization to either variable completely removed any significant association of the other variable to all forms of chronic respiratory disease.

Relative Risks

The greater relative risk of sickness and death from chronic respiratory disease in smokers as compared to nonsmokers has been reported in case-history studies of patients with chronic bronchitis and emphysema and by cohort studies.

In the present report the increased rates of disease have been expressed as relative risks on the basis of the rate in those who had never smoked as unity.

Pipe and cigar smokers were found to have a greater risk of disease than subjects who had never smoked tobacco. However, those who smoked cigarettes and a pipe or cigars did not have any increased risk of disease above that observed in cigarette smokers alone.

Certain evidence from this study supports the hypothesis that there may be a threshold beyond which cigarette smoking materially increases prevalence of chronic respiratory disease. The data indicate that it lies above 3,000 and below 9,000 packages or after eight years of cigarette smoking at the rate of between one and three packages a day. The precise threshold is not clear, and further studies are indicated.

The observation that cigarette smoking is clearly associated with the prevalence of chronic respiratory disease means that any demographic or epidemiologic study must standardize for its effect in some acceptable epidemiologic fashion. Nonsmokers may be the most suitable subjects in whom the effects of atmospheric pollution or occupational exposure to noxious dusts or gases should be studied.

Attenuated Live Virus Vaccination Against Measles

by

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Halifax, N. S.

In the United States of America, where measles mortality rates rank among the lowest in the world, it nevertheless causes more deaths than other communicable diseases of childhood. Conservative estimate indicate that approximately 500 children die each year as a direct result of infection with measles virus.

The quantity of gamma globulin employed to attenuate or prevent wild measles in family contacts in North America, presents a major problem of production since it necessitates the manufacture of over 4000 litres per year, which represents a substantial proportion of the entire production of North America.

The major complication of measles, namely encephalomyelitis, varies greatly in incidence from one epidemic to another, ranging from 1:400 cases to 1:3000 cases. Thus, when the total number of cases of measles is considered, this complication constitutes an important cause of viral encephalitis with all its attendant risks and undesirable sequelae.

During the winter of 1961, the Truro area of Nova Scotia alone, experienced an epidemic of measles, which the local physicians estimated to amount to about 1000 cases. Two cases of encephalitis occurred during this particular epidemic. In 1961, no less than six cases of measles encephalomyelitis were admitted to the wards of the Children's Hospital at Halifax, two of which died, and two showed signs of mental impairment. Both fatal cases occurred in children who were under the age of two years. Two of the children who were affected mentally were examined 18 months later, and continued to show evidence of serious mental retardation.

The true frequency of central nervous system complications such as slow learning and behavioural disturbances arising in later life, are perhaps not known, since it is difficult to assess the more subtle degrees of mental damage wrought by measles. There is a feeling among many that clinically severe, but uncomplicated measles, especially in younger children, may cause central nervous system impairment which is clinically inapparent at the time of the illness.

In this respect, Ojala (1947) examined the spinal fluids of 127 patients with measles, none of whom showed any clinical evidence of central nervous system involvement. He found a pleocytosis greater than 10 cells in 10% of the cases, occurring mainly between the 5th-10th day after the onset of the

rash, a time when the viremia of measles is over, but when overt encephalomyelitis often develops.

The most widely quoted study is that of Gibbs et al (1959) who performed electroencephalograms in 680 children with measles who did not show clinical evidence of encephalitis. Nevertheless, in this group, it was found that 51% showed what was considered to be abnormal tracings during the acute or immediate post-acute phase of the illness. There was a definite age incidence with younger children showing a proportionately higher incidence of abnormalities. In 1% of his cases, electroencephalographic changes persisted after recovery from measles. Gibbs et al (1959) also reported that E.E.G. changes were detectable in a smaller percentage of children with scarlet fever, rubella and chickenpox. His work has been criticized on the grounds that the changes after measles were non-specific and that similar transient changes may also occur in many other acute febrile illnesses. Apart from the effects of secondary bacterial infection, measles, *per se*, in the pre-viremic phase of the illness, produces an extensive acute inflammation of bronchial epithelium with interstitial pneumonia not infrequently occurring in the prodromal phase.

A severe and often fatal pneumonia may be caused by the virus especially in adults with leukemia or other malignancy and this is accompanied by extensive giant cell formation in the lungs. It is postulated that this rare complication occurs as a result of some immune deficit associated with the underlying disease. Cases of this type have occurred in the absence of rash or as long as 15 days after the rash has disappeared.

A point of special interest in the history of measles, as far as vaccination is concerned, is the fact that there have been very few case reports in world literature of overt encephalitis occurring in measles attenuated by gamma globulin. Riley (1958).

Soon after the original isolation of measles virus in human kidney tissue culture by Enders and Peebles (1954), experiments were inaugurated to try to attenuate the virus in order to produce a vaccine. The prospects for the development of a successful vaccine against measles were promising for the following reasons.

(1) Viremia is an important feature of the acute phase of the illness and therefore circulating antibody is an important component in the development of immunity to this disease.

(2) Measles is a single and relatively stable type of virus of universal distribution which possesses an apparently low or undetectable mutation rate.

(3) The encephalitogenic properties of a wild measles virus are greatly reduced in the process of attenuation by passage through the cells of an insusceptible host. This biological property is supported by the results of numerous animal experiments. Enders et al (1961).

(4) Respiratory involvement is an important part of the disease, so that any immunity derived from a vaccine would have to be effective at the cellular as well as the humoral level. Thus the most potent vaccine is one which must produce a mild infection rather than a simple stimulation of antibody production.

In attenuating the measles virus, Enders et al (1961) adapted the virus to growth on chick embryo cells and by repeated passage was able to evolve a strain which succeeded in infecting and immunizing monkeys, but without production of measles. Enders' attenuated measles virus, named the Edmonston strain, has been the basis of all the vaccines so far manufactured in North

America and it is available for investigational study and clinical trials at present intwo forms, (1) attenuated "live", and (b) inactivated "killed" virus suspension.

(a) The first is a lyophilized live vaccine which is reconstituted with distilled water and is administered subcutaneously in a single dose of 0.25 - 0.5 cc. After reconstitution the product is only stable if it is stored in a freezer at 4.0°C or less. It will lose some of its potency in the domestic refrigerator, after two weeks.

(b) The second is the recently introduced "killed" (inactivated by formalin) vaccine produced in monkey kidney cells or chick embryo and given subcutaneously in a dose of 0.5 cc.

Apart from the Edmonston strain vaccines, there are several others currently under test. One is the Toyoshima et al (1960) live vaccine in Japan, which has been administered by nasal spray, and the others include the U.S.S.R. -58 and Leningrad-4 strains in Russia; live vaccines which are given subcutaneously in 3 doses. Zhdanov, Dosser, and Fadeeva (1961) and Smorodintsev et al (1961).

Experiments with the Enders vaccine using an oral or intranasal route of administration, have been disappointing. Some children have been successfully immunized in this manner, but in general, the results have been erratic, and present indications are that the injectable route will be the only reliable means of immunization. For details of the effectiveness of different routes of vaccination the reader is referred to the report of Black et al (1960).

The Japanese claim to have secured a high take with their vaccine, according to Okuno (1960-61).

Up to a period of 12 months ago, several thousands of infants and children had received the Enders vaccine, subcutaneously without any untoward effect, and many more have subsequently been immunized. The ages of the vaccinees have ranged from 2 months to 16 years. No encephalitic complications have been reported to follow the use of this vaccine. In one of the original vaccine trials, 23 children, ages 2 to 9 years who received the vaccine were studied with daily electroencephalograms but no changes were noted except in one child who had developed a concurrent respiratory infection. (Gibbs et al, 1959).

In all the initial trials it was found that live vaccine often produced a clinical infection closely resembling that of wild measles modified by gamma globulin. This occurred at any period from the 5th to the 16th day after vaccination. About 80% of all children under 5 years of age developed fever over 101°, and 10% had a fever over 103°. The duration of fever varied from 1 day to 8 days, with an average of 2.5 days. About 50% of all children also developed a faint pink macular rash lasting from 1-4 days. Koplik spots were rare. Conjunctivitis, coryza, and cough occurred in about 1/5th of all vaccinees. See Dolgin et al (1960). In these original trials, the investigators reported that illness produced was in no way more severe than the reaction following smallpox vaccination. In all trials to date with the vaccine alone, the clinical reaction rate has been higher in the younger age groups and much less frequent in those over seven years of age. In addition, one important fact has emerged, namely, that vaccination trials conducted during the cold winter months have produced more frequent clinical symptoms than those conducted during the summer months. (Markham et al 1961). This may be due to the prevalence of secondary bacterial and viral infections

during winter months. Future measles immunization programs with live virus should be performed in the summer months.

Since these initial trials began and involving several thousands of children, further experiments have been undertaken to attempt to increase the attenuation of the vaccine virus, without altering its antigenic potency. For example, in one recently developed vaccine, the virus has been highly attenuated by 77 passages through chick embryo cultures. Schwarz (1961) recently reported a trial of this vaccine in 70 children in whom only two developed a rash, and no children developed fever over 100.7°. In these children 97% developed a good antibody response.

Experience gained in current trials has indicated that the antibody conversion rate has been over 95% with Enders vaccine, and no children so immunized, have developed measles after exposure to natural infection. The Russian "Leningrad-4" vaccine is less effective and only 80% responded with satisfactory antibody levels after 3 doses of the vaccine were given subcutaneously, according to Smorodintsev et al (1960).

Krugman et al (1960) reported the symptoms of vaccination could be still further attenuated by the simultaneous administration of gamma globulin in low dosage. Less than 1/5th of all children immunized in this way develop clinical symptoms, with no reduction in immune response. Subsequent further trials of this type have produced similar results. (See Kress et al 1961, and McCrumb et al (1961). The vaccine and the gamma globulin can be given simultaneously but at different sites of injection. Vaccination is ineffective if virus and gamma globulin are mixed together, and given in a single syringe. (Hilleman et al 1961). Two injections are therefore necessary. The amount of gamma globulin required is very small and as little as 0.01 cc/lb. is sufficient to produce subclinical infection. Ordinary pooled human gamma globulin may be used possessing an average measles neutralizing titre of 1:400. This procedure was followed in the Halifax trial.

Hilleman et al (1961) investigated the effect of substituting inactivated measles vaccine for gamma globulin as an initial antibody stimulating antigen in order to conserve the use of gamma globulin. In common with the findings, of others, Karelitz and Peck (1961) observed that three injections of inactivated vaccine, given at one month intervals, were necessary to eliminate clinical reaction from the live vaccine when given several months later. One injection is inadequate to cause a significant degree of clinical attenuation. In order to conserve gamma globulin for other purposes, the preliminary use of killed measles vaccine may constitute the future immunization technique of choice. The inactivated vaccine does not produce any apparent reaction.

Contraindications to the use of live measles vaccine seem to be relatively few. A number of investigators have conducted trials in children afflicted with various long-term illnesses, including cystic fibrosis (Shwachman et al 1961), asthmatic children, Kempe (1961), cardiac patients, Curnen et al (1961), and malnourished infants with incipient kwashiorkor by Katz et al (1961). In the latter study, malnourished children had a higher frequency of reaction to the vaccine but in no way more severe than those elicited in normal children. The only definite medical contraindication so far would appear to be in acute leukemia where protracted reactions may develop. One case of giant cell pneumonia has been reported by Mitus et al (1961) in a leukaemic child after vaccination. The same may be true in dysgammaglobulinemias, but no information is as yet available on this point.

Infants do not respond to vaccination under the protection of maternal antibodies and consistent antibody responses are not evoked until after the age of 8 months. (Blattner, 1961). Attenuated measles caused by the vaccine virus does not spread to contacts.

RESULTS OF CLINICAL TRIAL

Studies at Halifax.

The vaccine used in our tests was one originally derived from the Edmonston strain of measles virus, adapted to chick embryo culture by Dr. John Enders of Harvard University. (See Enders et al 1961) and (Katz et al 1961). Vaccine was prepared from the thirteenth chick embryo passage level* and kept frozen until it was rehydrated prior to use by addition of 1.0 cc of physiological saline. A dose of 0.25 cc. was given subcutaneously. (See Dolgin et al 1960).

In 1962, a total of 31 children ranging in age from 1 - 6 years, drawn from three Halifax Institutions were vaccinated with attenuated live virus. All were first screened for the presence of neutralizing antibody to measles. A serum antibody titre level of 1:4 or less was considered as evidence of susceptibility. Of the 31 children, 27 were found to be susceptible according to this standard. In this group we did not vaccinate children with a prior history of seizures. Blood serum neutralizing antibody levels were determined in children prior to and 6 weeks after immunization.

After vaccination, the children were examined daily for the presence of fever, cough, coryza, conjunctivitis, rash, lymphadenopathy and Koplik's spots. No local reactions to the vaccine were observed.

There were three groups, the first group constituted 8 children, ages 2 - 11, who received the vaccine alone. The second group of vaccinees, ages 1 - 16, received the vaccine plus gamma globulin in a dose of 0.01 cc /lb. The third group, ages 1 - 16, received vaccine and a slightly higher dose of gamma globulin, 0.02 cc /lb. (See Table I).

Table I

Vaccinated Children

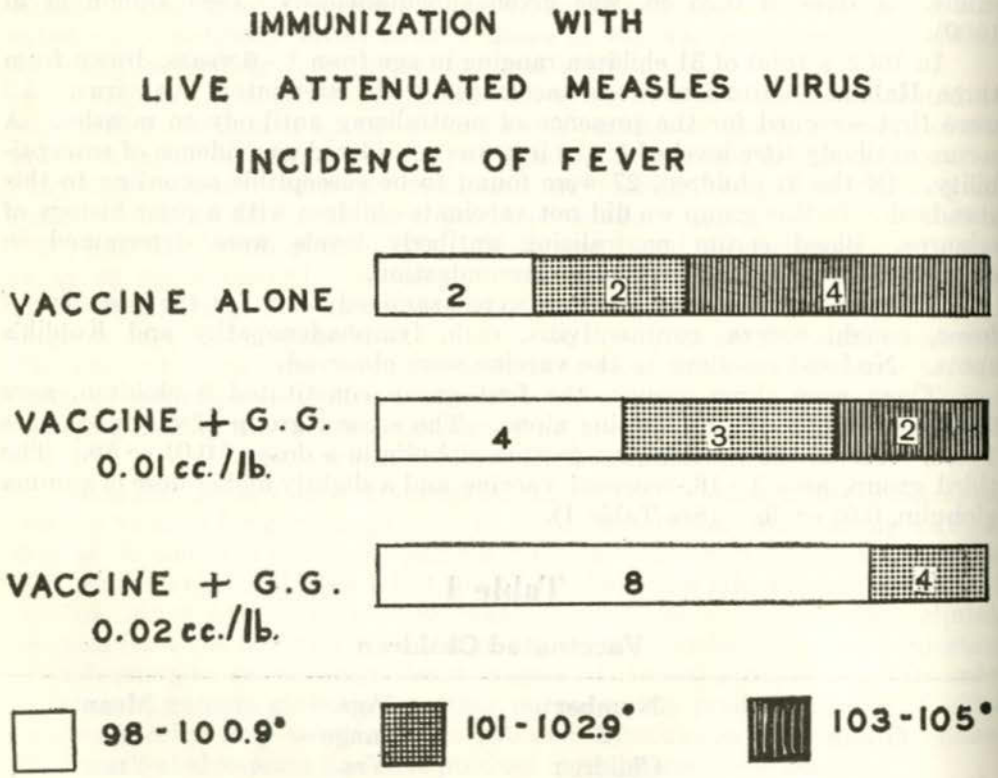
Group	Number of Children	Age Range Yrs.	Mean Age Yrs.
Vaccine Alone	8 (25%)	2 - 11	6.0
Vaccine+ G.G 0.01 cc /lb	12 (39%)	1 - 16	7.5
Vaccine+ G.G 0.02 cc /lb	11 (36%)	1 - 16	7.5

*Supplied through courtesy of Dr. J. M. Ruegsegger of the Lederle Division of American Cyanamid, Pearl River, N.Y.

Those children who developed symptoms, did so between 6 - 13 days after vaccination, and these consisted chiefly of transient fever and rash. Respiratory symptoms such as cough, coryza and conjunctivitis did not occur except in one institution where a concurrent upper respiratory infection was prevalent at the time of vaccination.

Fever. Six out of eight children developed fever after receiving the vaccine alone. Of these, 4 had a rectal temperature over 103°, lasting 2-5 days, and one child had a temperature of 105° for part of one day. (See Fig. 1). None of the children seemed to be incapacitated by the fever, and did not appear to be more affected than after anti-smallpox vaccination.

Figure 1



With the *lower dose of gamma globulin*, 0.01 cc/lb. 5 children out of 9 developed fever with only two having a temperature over 103°.

With the *higher dose of gamma globulin*, 0.02 cc/lb., 4 out of 12 developed a temperature of 101° or higher, but the duration of fever was only an average of 2 days. None of these children appeared ill at the time.

Rash. All 4 children who developed fever after vaccination without gamma globulin attenuation, also developed a faint macular rash, lasting 1-4 days. (See Table II). The incidence of rash was reduced in both groups who received gamma globulin. *The incubation period* was also slightly prolonged in those receiving gamma globulin. *Koplik spots.* There was only one child in which such lesions were evident.

Table II

Immunization with Live Attenuated Measles Virus Comparative Incidence of Rash

Group	Number of Children	Number with Rash	Mean Day Onset	Mean Days Duration
Vaccine Alone	8	4	10.5	2.5
Vaccine + G.G 0.01. cc./lb	9	1	12	2.5
Vaccine + G.G 0.02 cc./lb	10	2	13.5	1.5

Figure 2

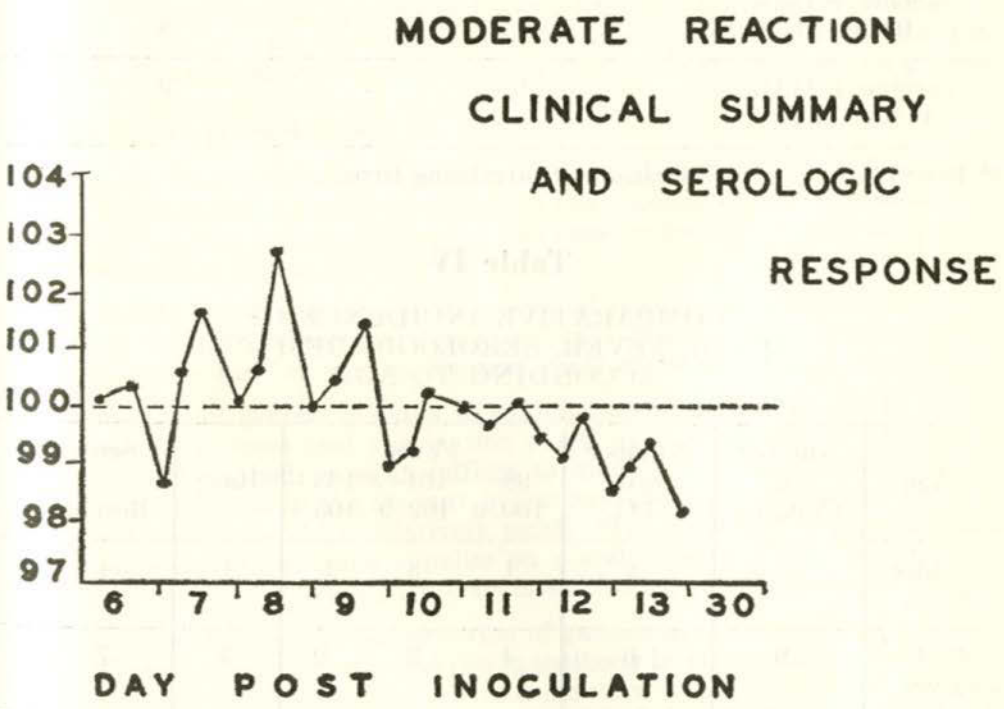


Figure 2 shows the course of a typical reaction in a child receiving live virus vaccine. Temperature persisted for 6 days; rash appeared on the 4th day of fever and lasted for 3 days. No upper respiratory symptoms were

observed. We also noticed that young children (irrespective of the use of gamma globulin) reacted more briskly to the vaccine than did older children. Good serologic responses were observed and a 4-fold or greater rise in titre was recorded in the group receiving virus alone. Slightly lower titres were found in those children who received gamma globulin. (See Table III). In all instances, the levels attained were comparable to that usually recorded after an attack of naturally occurring virulent measles. (See Table IV).

Table III

IMMUNIZATION WITH
LIVE ATTENUATED MEASLES VIRUS
SEROLOGIC RESPONSE

Group	Children without Initial Antibodies	
	Number	Number Responding*
Vaccine Alone	8	8
Vaccine + G.G. 0.01cc./lb.	8	8
Vaccine + G.G. 0.02cc./lb.	9	9

* Four fold or greater increase in neutralizing titre.

Table IV

COMPARATIVE INCIDENCE OF
RASH, FEVER, SEROLOGIC RESPONSE
ACCORDING TO AGE

Age	Number of Children	Number with G.G.	Fever			Rash	Serologic Response
			98–100.9	101–102.9	103–105		
Under 3 yrs.	5	4	1	3	1	1	4
Under 7 yrs.	9	6	4	3	2	3	7
Over 7 yrs.	10	12	9	1	2	3	8

Our preliminary observations support the contention of many other workers who believe that a small dose of gamma globulin will attenuate the post vaccination reaction to a degree sufficient to render it acceptable to most parents. According to Stokes et al (1960-61) if vaccination plus gamma globulin were restricted to the one year old age group, due to the light weight of this group, the demand for gamma globulin would be greatly reduced and result in a saving of about 2000 litres per year.

Possible spread of infection among vaccinees.

At three institutions where children were vaccinated with attenuated live measles vaccine, there was no evidence of the spread of infection susceptible close contacts. (See Katz et al 1960).

Protective efficacy. Our observations are still incomplete. At one large institution, an outbreak of measles occurred some 12 months after we had vaccinated 6 children with live virus plus gamma globulin, but it was interesting to note that these 6 children escaped infection.

Use of inactivated dead measles vaccine.

To circumvent the shortage of gamma globulin, killed vaccine has been employed as a substitute method for producing an initial level of active immunity. 31 children are being immunized by this method and the vaccine given subcutaneously at one month intervals. No reactions have been observed and such immunization appears to be well tolerated by delicate children. It remains to be proved, however, if such vaccination will evoke an adequate level of antigenic stimulus comparable to that confirmed by gamma globulin.

Summary and Conclusions

1. 31 children have been successfully vaccinated with attenuated live measles virus vaccine. No serious reactions were encountered in this small series A successful antigenic response and some encouraging signs of apparent protective effects were noted.

2. 15 other children were given a dose of inactivated dead virus vaccine and no obvious reactions were observed. Tests on the antigenic response following the first and subsequent doses of vaccine are in progress.

3. The use of gamma globulin in conjunction with live attenuated measles vaccine reduces post vaccination reactions to a minimum. As little as 0.01 ml/lb. body weight suffices to modify live virus vaccination and on a weight basis the amount of gamma globulin required to protect a one year old child is relatively small. The difficulty of obtaining adequate gamma globulin supplies on a scale adequate for the conduct of mass vaccination campaigns against measles, is appreciated.

4. Due to the need for conservation of gamma globulin supplies, the possibility of producing an initial rise in antibody level by substitution of killed measles virus vaccine for gamma globulin is being explored. Further work is being directed along these lines and the effect of 3 doses of killed virus vaccine as a substitute for gamma globulin is under test.

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NOTICE TO MEMBERS

At the meeting of the Executive Committee December 1st, 1962 the following resolution was carried:

"THAT notice of motion be given to the Annual Meeting of The Medical Society of Nova Scotia that practitioners resident in the province of Nova Scotia be required to be members of The Medical Society of Nova Scotia before they can be participating physicians in Maritime Medical Care, Incorporated."

Case Report

Congenital Biliary Atresia in Identical Twins

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Amherst, N. S.

The mother, age 20, has been healthy throughout her life and, apart from childhood complaints, has had no serious illnesses. She has had no radiotherapy except for routine chest X-ray and has had no obvious contact with ionizing radiation or radioactive isotopes.

The father is a healthy man and has had no serious illnesses. There is no family history of congenital anomalies occurring on either side of the family.

The mother first became pregnant in 1957 and delivered a normal male infant in 1958 following an uncomplicated pregnancy. The mother became pregnant for the second time in 1959 and the pregnancy proceeded uneventfully except for premature labor starting at 7 P.M. June 19, 1960. Her expected date of delivery was July 11, 1960. She was admitted to Sackville Memorial Hospital in advanced labor at 10:15 P.M. she delivered a small male child (twin A) at 10:53 P.M. and a second small male child (twin B) at 10:57 P.M. The mother was Rh positive, Hgb. 71%. She had an uneventful post partum course.

Twin A (G.F.W.), birth weight 4 lbs. 14 oz. Supportive treatment with oxygen in Isolette for first three days. Discharged from hospital July 29, 1960, weight 6 lbs. 3-3/4 oz. Twin A was first seen by myself on August 30, 1960 with a history of a stuffy nose. Examination revealed a small infant with a white nasal discharge, chest clear to I.P.P.A., temperature normal. Triple sulfa suspension given for an upper respiratory infection. Next seen on Labor day Sept. 5th. The mother stated that his cold had improved and that he appeared to be doing well the night before when put to bed. The infant had died suddenly during the night. It was decided that an autopsy was necessary. Apart from the usual indications for autopsy of sudden death in infancy, it was necessary to assist treatment of maternal guilt complex and also the other twin (B) was developing similar symptons.

Twin B (G.E.W.), was admitted to Highland View hospital Sept. 6, 1960 complaining of stuffy nose with difficulty in breathing, anorexia, occasional cough and fussiness. Past history - born prematurely June 19, 1960. Birth weight 4 lbs. 5 oz., supportive treatment with oxygen in Isolette for first three days. Discharged from Sackville Memorial hospital July 29, 1960, weight 5 lbs. 9 oz. Home on babies formula, evaporated milk 9 oz., sterile water 14 oz., dextrimaltose No. 1, 2 tbsp., rice pablum 1 tbsp. twice a day. History of present illness – Since coming home from hospital he has had a stuffy nose which has gotten worse since Sept. 2nd. Patient has become cranky and developed an occasional cough.

Physical examination – revealed a small three month old infant well nourished but having some respiratory difficulty with intercostal indrawing. Respirations 48/min. There was mild rigidity of the neck and in flexing the

hips. Scattered rhonchi over the chest with occasional rales. Heart rate fast 200 / min. Impression – upper respiratory infection.

Progress in hospital:

Sept. 7/60: Neck rigidity improved, mildly jaundiced, rhonchi over chest, Hgb. 61%, WBC 17,300, urine trace sugar, temp. 100° (R), chest X-ray reported as negative.

„ 8 : Stool very foul smelling, brighter but still stuffy nose, blood film: eosin. 1%, stabs. 3%, segs. 30%, lymphs. 63%, monos. 3%, RBC's hypochromic various size and shape, platelets appear normal, there is rare polychromasia, formula taken slowly. Throat swab reported light growth of staphylococcus pyogenes only, sensitive to penicillin.

„ 9 : Repeat urinalysis shows a trace of sugar, bile 4 plus, jaundice is variable, stool white clay colored, stool culture is neg., occasional rhonchi over the chest with rattling breathing.

„ 10 : Patient content and appetite improved, stool grayish color, urine bile 1 plus, urobilinogen negative.

„ 11 : Occasional rhonchi in the chest, large pasty looking stool.

„ 12 : Weight 8 lbs. 10 oz.

„ 13 : Stools clay color and 1 normal yellow, liver function blood tests: CCF neg., alkaline phosphatase 65.5 (King Armstrong units) thymol turbidity 1.4 units (N O.4), zinc sulphate 1.9 kunkle units (N 2-8), S.G.O.T. 43 units, S.G.P.T. 41 units, bilirubin total 3.8 mg.%; direct 1.1 mg.%; indirect 2.7 mg.%.

„ 14 : Appetite good.

„ 15 : Soft yellow stool.

„ 16 : Nasal congestion.

„ 17 : Urine urobilinogen – neg., temperature normal.

„ 18 : Loose stools with flatus, temperature 100.4°(R)

„ 19 : Temperature 99.6, urinalysis acid, bile 4 plus, sugar negative, WBC 24,950, Hgb. 60% (9.4 gms.).

„ 21 : Temp. 102°(R).

„ 22 : Quite irritable, urine bile 2 plus, urobilinogen-neg, awaiting transfer to Halifax Children's hospital.

„ 23 : Taking formula slowly.

„ 24 : Extremities rigid with some abdominal tenderness.

„ 25 : Lot of flatus, seems to have some abdominal pain, strong peristaltic pressure with bowel movements, temp. 104°(R).

„ 26 : Temp. 102°(R), listless, large green bowel movements.

Treatment in hospital consisted of:

Cryst. penicillin 200,000 units Q 3 hrs. x 4, then S.R. penicillin 300,000 units B.i.d.

Fer-in-sol 0.3 cc t.i.d., Sept. 8 taken off precautions, diet consisted of Perfection milk 12 oz., water 14 oz., honey 2 tbsp., given pablum, vegetables, meat and fruit p.r.n.

Sept. 20: discontinued penicillin, Sept. 26 started terramycin suspension.

Discharge summary:

Three month old twin, twin brother died suddenly during the night, admitted to the hospital with an upper respiratory infection. Throughout his hospital stay he showed a constant rhinitis and suffered from occasional foul smelling diarrhea and vomiting. As all the biochemical tests pointed to an obstructive cause for the jaundice he was transferred to the Halifax Children's hospital for consideration of possible surgery. The jaundice varied somewhat but never completely disappeared and the icterus of the skin underwent a greenish change. Physical examination at the Halifax Children's hospital revealed a pale infant with fever and a little lethargic, EENT - OK, chest – lungs clear to percussion and auscultation, heart – OK, liver – 1-2 fingers below costal margin, throat – normal flora.

Although jaundiced he appeared well on the evening of admission but was difficult to settle down for the night. Suddenly without warning at 3:30 in the morning he stopped breathing. Medical examination showed cardiac arrest as well. Attempts at resuscitation were unavailing. Final diagnosis was infectious hepatitis.

Autopsy report on Twin A (G.F.W.) –

Abnormal findings of the respiratory system: Lungs (right 46 grams – normal 34 grams; left 36.5 grams – normal 26 grams) lie free within the pleural cavities though neither is collapsed. The pleural surface is smooth and shiny but the underlying pulmonary parenchyma is dark reddish-purple on each side and subcrepitant. Serial sections through the lungs show a dark red slightly moist subcrepitant parenchyma without any localized regions of consolidation and no evident collapse. Microscopic sections of the lungs all show an intra-alveolar exudate composed of fibrin and large mononuclear macrophages compatible with viral pneumonitis.

The liver weighs 170 grams (normal 137 grams). It appears somewhat congested but not grossly so. There is no evident fatty change. The gall bladder contains a few drops of light green bile and the contents of the duodenum are bile stained.

Microscopic report of the liver –

Lobular architecture is maintained but there is gross dissociation of liver cell cords and slightly increased collagenous fibrous tissue within the portal triads. In addition there is almost complete absence of bile ducts except within some of the larger portal tracts where minute, grossly hypoplastic ill formed bile ducts are identifiable. Some of these appear to lack a lumen. There is very faint bile staining of some of the liver cells mainly in the centres of the lobules but this is not a pronounced feature. Scattered throughout the liver are small foci of extra-medullary haematopoeisis. The diagnosis of atresia of the small bile ducts and gross hypoplasia of the larger intrahepatic ducts must be added to the original autopsy report of pneumonitis of infancy, viral etiology. Bacteriological investigation did not reveal any significant bacteria and the rest of the pathology report was unremarkable.

Autopsy report on Twin B (G.E.W.) –

Pertinent autopsy findings: The body was that of a well-nourished, well-developed infant weighing 3,850 grams, measuring 37 cms from crown to rump. There was moderate greenish icterus of the skin. Lungs (right 54 grams – normal 35 grams), (left 45 grams – normal 30 grams). Neither lung

collapsed on opening the chest and both were deep pink, subcrepitant and rather meaty with a dry cut surface showing faintly outlined irregular greyish areas on the cut surface. The intervening regions being a deeper red but not intensely congested. A small amount of oedema fluid could be expressed on pressure.

Abdominal cavity –

The mesenteric lymph nodes were massively enlarged up to 1.2 cms. in length though they remained discrete one from the other.

The liver weighed 160 grams (normal 140 grams). It was smooth, greenish yellow with a rather blotchy appearance beneath the transparent capsule and , on the cut surface, an olive green generalized discolouration with irregular geographic regions of darker green and occasional zones suggestive of haemorrhage varying from 3 to 10 mm. in width. Situated posteriorly on the horizontal cut surface just anterior to the inferior vena cava at the junction of right and left lobes there was a roughly circular zone, very well demarcated from the rest of the liver, having a pale greyish-green periphery approximately 2 mm. wide and a central dark green, somewhat softer centre. The gallbladder contained approximately 3 ml. of clear mucoid bile which could be expressed easily into the duodenum and the extra-hepatic biliary tracts contained similar bile as far as they could be traced into the liver with fine scissors. There were no calculi. Bacteriological and virological study was done and no pathogens were obtained.

Microscopic report –

Liver – Sections from the right lobe of the liver show retained lobular architecture, dense bile staining of the centres of the lobules and plugging of biliary canaliculi with inspissated bile plugs. The smaller portal triads are completely devoid of bile ducts and in the larger ones there is, in general, gross hypoplasia varying from very small ones in the larger tracts to ill formed ones lacking a lumen or complete absence. Only in the largest interlobulary regions can well-formed bile ducts be seen and these are completely lacking in any bile content. Sections through the region of hepatic necrosis show complete dissociation of liver cells, intense bile staining, congestion, polymorphonuclear infiltration and large masses of inspissated bile. About the periphery of this region there is an early fibroblastic proliferation.

Left lobe of the liver – Only a minority of the portal tracts are devoid of bile ducts, most of them containing small hypoplastic ones which frequently are very ill formed and lack lumen. There is patchy bile stasis.

Lungs – All sections of both lungs are atelctatic, congested and many of the air spaces filled with oedema fluid. There is no evidence of pneumonia.

The rest of the examination is unremarkable. The autopsy showed hepatic changes similar to those in the twin brother, though of a slightly less severe degree, being mainly confined to the right lobe of the liver. Bile stasis was very much more marked than in the other infant and there was a large 1.5 cm. area of acute hepatic necrosis which probably was not of longer than three to four days duration.

Pathological diagnosis –

Atresia intra-hepatic bile ducts (small)
Hypoplasia intra-hepatic bile ducts (main)
Focal necrosis of the liver (right lobe)

Pulmonary atelectasis
Congestion of all viscera

Discussion –

A case of congenital atresia of the intra-hepatic bile ducts occurring in identical twins has been reported. None of the known predisposing factors to the development of congenital anomalies such as radiological pelvimetry, maternal rubella or exposure to ionizing radiations appear to exist in this case.

It is probable that genetic factors play an important causative part in this instance. This is especially true in this case since genetic make up in identical twins is, as far as we know, identical.

The presentation of this case may appear disjointed at times. The progression of events was presented in the order in which they occurred so the reader might appreciate the sequence, as it occurred in the twins, rather than having two separate presentations.

The autopsies were done by Dr. I. D. Maxwell, Department of Pathology, Pathological Institute, Halifax, N. S. Bacteriological studies were done by the Department of Bacteriology, Pathological Institute, Halifax, N. S. Virological studies were done by the Department of Biology, Pathological Institute, Halifax, N. S.

The Increased Importance of Auscultation in the Management of Heart Disease

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The history of medicine is one of advance at a varying pace. *While the enquiring and observant mind remains the most important factor in progress,* the introduction of a technique extending or simplifying the use of our senses, often results in accelerated improvement in our knowledge.

Such was the case 150 years ago when Laennec, discussing the use of his newly introduced stethoscope, referred to the "*dull rustling sound* very like the noise of a bellows, or when stronger like that produced by the action of a file on wood" resulting from "an obstacle in the auriculo-ventricular orifices". Careful clinical observations, and in particular their correlation with, and confirmation by *autopsy* findings, resulted over the subsequent hundred years in the development of auscultation as an empiric but relatively accurate diagnostic technique.

The *failure of cardiac therapy* to develop concurrently led many practitioners to question the value of making precise anatomical diagnoses of valvular disease or of congenital anomalies. This attitude was furthered by a *deviation of interest* from heart disease as control of infections became possible. *Auscultatory skills declined* and knowledge was lost. However, the control of infection permitted major extensions of surgery which in turn forced development of the truly remarkable anaesthetic techniques of to-day. As a result, *cardiac surgery has developed rapidly* to become not only an important palliative measure, but often a largely curative "plastic" or reconstructive procedure.

Early in the course of cardiac surgery, it became apparent that *then current standards of auscultation were too inaccurate* to provide necessary preoperative anatomical - physiological information. The new diagnostic techniques of cardiac catheterization and angio-cardiography were introduced, but are not too readily available. However these newer techniques were applied also to clinical-physiological studies of auscultation, markedly accelerating a renewed interest in heart sounds that had been developing since the introduction of the electrocardiogram and the phono-cardiogram, and advancing our knowledge beyond the best available from the older clinico-pathological correlations. As a result, *it is now possible to provide an accurate anatomical and physiological diagnosis in the practitioners office in 75% to 80% of instances* where a heart murmur is heard.

However, this knowledge has not reached the practitioner and is not being applied in patient care. 593 physicians attempting diagnosis of 15 tape recorded commonly heard normal and pathological heart sounds and murmurs, at the American Medical Association meeting in 1959, achieved *only 49% accuracy.* How can each of us move from this grossly inadequate level of current average performance to the level of reasonable competence that will give us up to 75% accuracy in auscultatory diagnosis?

Any one who, listening to an orchestra, can learn to identify the contribution of a single instrument (for example, a French horn), is capable of becoming a skilled cardiac auscultator. Knowledge of the basic factors involved in the

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production of heart sounds, and of the modifying influences of the thorax, the stethoscope, and the human ear, is now easy to attain. The opportunity to apply this new knowledge, presents itself with every patient seen.

A few points in connection with the physiology of hearing are helpful. The sensitivity of the ear varies at different frequencies, being greatest in the voice range, decreasing both in the higher and lower levels. It is *possible to focus* on a single sound at the cerebral level, and by this means detect it when otherwise it cannot be heard. This process is facilitated by lack of extraneous noise. Both practice at listening for individual sounds, and the selection of a quiet environment are important because *heart sounds are of low frequency* (many being inaudible under even ideal conditions).

The stethoscope should allow essentially all the sound energy present at the skin surface to reach the ear drum. This is facilitated by a short (10 inch) direct, smooth wall tube of about 4 mm. diameter, free of any air leaks, that is – fitting the air canal exactly. This is rarely achieved in to-day's stethoscopes. A bell is necessary for proper detection of low frequency sounds as the diaphragm attenuates sounds under about 100 cycles per second.

The *technique* of auscultation, forgotten by most of the few fortunate enough to have learned it at all, is most important. *By orienting oneself in time, and dealing with one sound at a time*, even the most complex findings can be recorded accurately, then analysed at leisure. In summary, the apex beat or carotid pulse identifies *the first sound.* Its audible portions result from closure vibrations in the mitral and tricuspid valves, occurring asynchronously so that the sound is usually muffled and, rarely, mid-way between the apex and base of the sternum, closely split. The *second sound*, shorter, higher pitched, and best heard adjacent to the sternum, is produced by the asynchronous closure of the aortic and pulmonary valves, and is usually split - the degree varying with respiration The *third heart sound* is low in pitch and intensity, resulting probably from sudden tensing of the ventricular muscle, by the inflow of a bolus of blood from the atrium, early in diastole. It is heard only in children and slender young adults, unless accentuated by disease. The *fourth heart sound*, generated by the atrium, is normally inaudible.

Other cardiac sounds fall into three categories: *Clicks*, *Frictions*, and *Murmurs.* The clicks in systole are either in early or mid phase. The former are intra-vascular in origin, occurring in the proximal aorta and the pulmonary artery when these vessels are suddenly dilated by the ejection of blood into them. They are audible only when ejection is forceful, as in hypertension, or the vessel is dilated; and are called *"Ejection Clicks"*. *"Mid-systolic clicks"* are probably pericardial in origin, entirely innocent, but often mis-diagnosed as systolic murmurs with unnecessary denial of insurance or chosen employment resulting. Diastolic sounds include the diagnostically very important *mitral opening snap*, audible only in mitral stenosis. This is high pitched, following the second sound closely, and far easier to hear than the classical mid-diastolic murmur. The other important diastolic sound is the ominous *diastolic gallop* – a third heart sound accentuated by dilation of the acutely failing left ventricle. *Frictions* are characteristically systolic and diastolic, medium to high pitched, and superficial; sounding closer to the ear than are the heart sounds in the background.

Murmurs become most informative when considered from several points of view. They should be *timed*, not only into systolic and diastolic types, but also into early, mid, or late phase murmurs. *Duration* is of particular import-

ance, e.g. in differentiating the aortic, stenotic, and mitral regurgitant systolic murmurs, as the former is often well heard or even best heard at the apex rather than at the base. In fact *location* of the murmur is now considered a rather poor criterion of its origin.

Intensity of murmurs most logically described as faint, moderately loud, loud, or very loud, is unfortunately being more and more widely recorded in a pseudo quantitative medical shorthand (Grade I to Grade 6). Descriptions of *pitch* are difficult to learn because of a discrepancy with music. In recent years the musical note "A" has been assigned a frequency of 440 cycles per second, and middle "C" has one of 256 cycles per second, both generally considered to be medium pitches. Heart sounds of 30 to 80 cycles per second are considered low pitched; those of 80 to 120 cycles per second, medium pitched; and those over 120 cycles per second, high pitched. This is obviously a relative scale. *Quality* can be *learned* better than described, and does much to identify murmurs, as already mentioned in connection with duration, far more accurately than location.

Perhaps the most important *systolic* murmur to recognize, being the commonest, is the *non-pathological innocent* or *functional* one. It is usually not loud, and of short duration, either early, mid, or late phase. Because of considerable variability however, it is best categorized only after consideration of the entire history, physical examination, X-ray and electrocardiographic study of the heart, all of which are normal; and some times only after repeated examinations of the patient at extended intervals.

This total approach to cardiac diagnosis is, of course, the proper one in all circumstances, but the *pathological murmurs* accurately categorized by the already suggested auscultatory techniques, are often diagnostic. Leatham has divided the systolic murmurs into two types – *ejection and regurgitant.* The ejection murmur is a crescendo – decrescendo – long, early and mid systolic murmur of low to medium pitch, which ceases before the second sound. The regurgitant murmur is a uniformly loud, medium to high-pitched pan-systolic murmur occupying the entire interval from first to seond sound. The ejection murmur regardless of its place of maximum loudness, indicates turbulence in the pulmonary or aortic areas which may result from rapid flow, large volume flow, flow across a damaged valve or into a damaged major artery, with usually a low pressure differential. The regurgitant murmur results from the flow of blood under a high-pressure gradient, its turbulence producing an impressively loud murmur from even a small volume flow of blood. This usually occurs across a damaged mitral valve, but can of course result with normal valves but dilated valve ring, and also at the tricuspid valve or through a ventricular septal defect.

The *diastolic murmurs* are, in almost all instances pathological. There are two main types. The *early diastolic* murmur is similar to the pan-systolic murmur, being high pitched as the result of blood flow between two chambers of widely different pressures. It is characteristically heard low in the sternal area in patients with aortic regurgitation. The other type of diastolic murmur is similar in its genesis to the systolic ejection murmur, resulting from the flow of blood at low pressure, so that it is low pitched and rumbling. This classic *mid-diastolic murmur* is, of course, that of mitral stenosis. Characteristically it is preceded by the mitral opening snap, and blends into a late diastolic)presystolic) crescendo murmur prior to the accentuated first heart sound.

The continuous murmur of patent ductus tends to be over diagnosed. A

venous hum which can be differentiated by its cessation when the jugulars are compressed, or its diminuation when the patient lies down, is often mistaken for the murmur of patent ductus.

In Summary: I have attempted to indicate that advances in cardiac auscultation provide the general practitioner a simple, accurate, and commonly useful diagnostic team – his own trained ear and a proper stethoscope; the only cost being a careful study of the basic principles, and repeated practice.

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BOOK REVIEW

Practical Anaesthesiology. By J. F. Artusio and V. D. B. Mazzia. Published by The C. V. Mosby Company, St. Louis, Mo., 1962. 307 pages. Price $7.75.

Any specialist in teaching his subject to non-specialists is liable either to oversimplify or to assume too much technical knowledge in his audience. Practical Anaesthesiology, the authors state, is designed for medical students and general practitioners as a handbook of current practice in Anaesthesia. Doctors Artusio and Mazzia have succeeded admirably in avoiding both the pitfalls of teaching and have set out in a plain, straightforward and workmanlike manner much of the essential basic principles of Anaesthesia.

Inevitably, in a short presentation such as this, there is a tendency to be dogmatic but in the majority of instances this occurs mainly in emphasizing points of safety. In addition, the suggested reading at the end of each chapter will go far towards correcting any deficiency in controversial matter.

The book is extremely well written and very readable, and the authors have avoided the repetition which is so often seen in manuals for students. Its refreshing restatement of basic principles allows me to recommend it not only to medical students and general practitioners, but also to the specialist Anaesthetist who is concerned in teaching

Personal Interest Notes

Owing

TO The Nova Scotia Medical Society of N. S., by the DIVISIONS of the Society throughout the Province - the sums of four or five cents respectively, monthly - being the return postage provided each SECRETARY in expectation of vast DIVIDEND yield in PERSONAL INTEREST NOTES. DEBT overdue but may be CANCELLED. - easily.

Doctors in the News

Amherst

Dr. Edmund Ryan has been appointed psychiatrist for the clinic to be established by the local branch of the Canadian Mental Health Association. For this area the clinic centre will be in the MacQueen residence of Highland-View Hospital.

Dr. Ryan comes to Amherst from St. John's, Newfoundland.

Digby

On May 14, 1963, Dr. J. R. MacCleave, whose son Graham graduated in Medicine from Dalhousie on May 16, and made him a grandfather on May 25 - in his capacity as chief of the Digby General Hospital Medical Staff, turned the first sod in the construction of a new 90 bed, $1,600,000.00 replacement hospital. (Congratulations all around.)

Halifax

A two day conference on emergency health services was held recently at Camp Hill Hospital. More than 35 sanitary inspectors from various parts of the province heard Dr. S. H. Kryszek, director of emergency health services for Nova Scotia speak on "The Role of the Sanitary Inspector in Disaster". "Winter Hygiene and Sanitation" was discussed by Dr. P. C. Gordon of Halifax. "Dr. G. M. Smith of Windsor spoke on "The Public Health Unit and Disaster."

The Atlantic Division of the Canadian Heart Foundation has, for the sixth successive year donated $3000.00 to the Post-Graduate Division of the Faculty of Medicine at Dalhousie. Dr. C. B. Stewart, Dean of Medicine received the check from Dr. J. M. C. Duckworth, Atlantic Director of the Foundation. The contribution is to be used in support of post-graduate education in cardiovascular disease. In recent years about 10% of the programme of the postgraduate division of the medical school has been devoted to cardiovascular diseases.

A framed, illuminated scroll was presented to Dr. H. B. Atlee by the Commissioner of the Salvation Army at the official opening of the extensive modern addition to the Grace Maternity Hospital, on May 22, in recognition

of his efforts over the last forty years to improve the standards of maternity care in this community.

Dr. Atlee made headlines again on May 31 in the report of his speech to the Conference on The Child, held on that day. He spoke on "Education - Where Are You?" His answer was succintly - not where it's needed.

Upper Stewiacke

To aid in our constant fight against cancer, Dr. M. C. Bell was in attendance at the recent showing of two films for women only in the Community Hall at Upper Stewiacke on May 28. There was a good attendance of women from Middle Stewiacke to Easville and the surrounding district.

Births

To Dr. and Mrs. Graham McCleave, (née Louise Atkinson), a daughter, Heather Louise, at the Grace Maternity Hospital on May 25, 1963.

To Dr. and Mrs. Carl MacDonald (née Shirley MacDonald) at the Grace Maternity Hospital, on April 28, 1963.

To Dr. and Mrs. Bruce MacWhirter (née Anne Summers), a daughter, Stephanie Dorothy, at the Grace Maternity Hospital on May 4, 1963.

Congratulations

To Dr. William Clyde Nicholas, who so recently was congratulated on obtaining his fellowship, on the announcement of his engagement to Miss Sheila Marie Bonnell, daughter of Mr. and Mrs. John R. Bonnell of Sydney. His marriage will take place in Sydney on June 29th.

To Dr. John E. Campbell of Halifax, who received his Diploma in Radiology from McGill University on May 31st.

To Dr. E. M. Fogo whose appointment as Halifax City Commissioner of Public Health has been recommended to council. The appointment is to fill the vacancy created by the resignation of Dr. A. R. Morton because of ill health. Dr. Fogo has been acting commissioner for the past one and a half months.

To Dr. J. G. Holland, son of Dr. Clyde Holland who at the Dalhousie Convocation received his medical degree, winning the University Gold Medal in Medicine, (as his father did before him), and also the Ross Stewart Smith Fellowship in Medical Research.

To Miss Vivian Boniuk fourth year medical student who won the prize for the highest aggregate in the examination of the fourth year as well as prizes for the highest standing in Surgery, Obstetrics and in Psychiatry.

To Dr. H. C. Read, Associate Professor of Medicine, Dalhousie who has been awarded a grant by the Canadian Arthritis and Rheumatism Society. It is part of a $300,000.00 programme of grants for research into the structure of connective tissue involved in arthritic and rheumatic diseases.

To Dr. Lalia Chase, who at a gathering of the Girl Guides and Leaders of King's Co., Mrs. by E. L. Rand, camp adviser presented Dr. Chase with a LIFE MEMBERSHIP in the Girl Guides of Canada. The presentation honoured her aid in establishing the Guide Camp at Hardwood Lake.

Forthcoming Meetings and Arrangements

CHECK-UP: Factual Medical Series on CBC-TV NETWORK: STARTS: JULY 8. A 12-week series featuring practising doctors across Canada, starts MONDAY, JULY 8, at **7.30 p.m.** E.D.T. on the CBC-TV network.

The series produced by the CBC in cooperation with the Canadian Medical Association will show present day methods of diagnosis and treatment for various illnesses and complaints. Its purpose is to show how a doctor manages common ailments, to emphasize the role of the responsible patient, to help people to take better care of themselves show them how to use a doctor's time and services to the best advantage.

SUBJECTS: Rheumatoid arthritis, backache, cancer (leukaemia), coronary heart disease, chronic cough, allergy, geriatrics, prenatal care, anxiety tension, diabetes, accidental poisoning in children, and headache.

LOCAL DOCTOR taking part - Dr. H. R. Philips, member of College of General Practice, Halifax, - "Chronic Cough."

A THREE-DAY SCIENTIFIC CONVENTION - with special after lecture attention to recreation - is being organized by the Ontario Chapter of the College of General Practice, to take place at Prudhommes Garden Centre in the Niagara District. TIME: Oct. 1, 2, 3. All general practitioners are invited to attend whether they are members of the College or not.

THE CANADIAN CARDIOVASCULAR SOCIETY and the CANADIAN HEART FOUNDATION are holding joint ANNUAL AND SCIENTIFIC MEETINGS IN TORONTO November 20-23, 1963.

Address inquiries to Dr. J. B. Armstrong, Canadian Heart Foundation, 501 Yonge St., Toronto 5.

Medical Group Tours

Medical groups are being formed in Canada and U.S.A. for a tour to include medical events in Central and Southern Europe:

1) IXth International Congress of Orthopaedic Surgery and Traumatology - Vienna - Sept 1-6.
2) XXth Congress of the International Society of Surgery - Rome - Sept. 16-21.
3) Congress of International Cardiovascular Society - Rome - Sept. 19-21.
4) International Conference on Cardiology - Athens - Sept. 14th.

A tour of the Greek Islands including Kos - the birthplace of Hippocrates - takes the group beyond Athens, and the usual tour activities are being arranged for other cities.

This is becoming a popular way for doctors to extend their knowledge. Last year's tour to the VIIIth International Cancer Congress was very successful, and there is even wider interest in this.

Dr. N. H. Gosse of Halifax has again consented to assist in the formation of groups from this area interested in attending these Medical Tours as he did last year. The A. Nirenberg Travel Bureau Ltd., of Montreal, and K.L.M. Airlines are the Companies directly involved.

A good feature of the project is that no "charter flights" are involved. Groups are kept to 25 persons and travel is on scheduled planes.

PATHOLOGICAL FINDINGS IN ACUTE PORPHYRIA

A study was undertaken recently at the Mayo Clinic to investigate the pathological findings associated with acute porphyria. Nine patients, all male, who were adjusted clinically and biochemically to have had acute porphyria were studied by Ten Eyck, Martin and Kernohan (Proc. Staff Meetings Mayo Clinic 36:409, 1961) Barbituates had been administered to eight of them. A family history of porphyria was likely in one and possible in two. Seven had associated potentially fatal disorders.

Abdominal pain, which occurred in five of these patients, is a prominent manifestation of acute porphyria. The pain is frequently severe and may be localized or generalized; there may be associated nausea, vomiting, and obstinate constipation. Jaundice is rare; in two patients who had jaundice, other diseases could have been responsible for the finding.

Neurologic manifestations vary from motor weakness to flaccid paralysis. Paralysis was noted in four of the nine cases. Although paresthesia occurred in one case, it may have reflected periarteritis nodosa. Areflexia may occur, but objective sensory changes are rare. Convulsions, as occurred in three of our patients, and visual disturbances which also occurred in three patients, are not uncommon. A hoarse, whispered voice was described in another case. Bulbar involvement with respiratory dysfunction occurred in three of our patients. Rarely is the pressure or protein content of the cerebrospinal fluid increased as in two cases. Mental changes are frequent, as exemplified in three cases. Hypertension and tachycardia, which were noted in half of these cases, also characterize acute exacerbations. Fever may occur but, like leukocytosis, it may reflect complications.

Although the urine is porphyria frequently is discolored, freshly voided urine may be colorless. Acute porphyria is characterized by the urinary excretion of delta-aminolevulinic acid, porphobilinogen. Waldenstrom's iroporphyrin, and increased amounts of coproporphyrin, especially type III. Delta-aminolevulinic acid is a precursor of porphobilinogen, and detection of either compound is highly suggestive of porphyria. Urinary uroporphyrin normally occurs in amounts of 5 to 20 micrograms per 24 hours; however, except in heavy-metal intoxication, its detection by qualitative methods suggests porphyria. Coproporphyrin normally occurs in the urine (100 to 300 micrograms per 24 hours) and feces (300 to 1100 micrograms per 24 hours); it is increased in conditions other than porphyria.

Barbituates have long been thought to cause exacerbations of acute porphyria; such a history was obtained in eight of the nine patients. In two patients exacerbation followed operations during which pentothal anesthesia had been used. The incidence of acute porphyria is greater in women; it is striking that all nine patients in this study were men. As is true of hypertention and pyelonephritis, acute porphyria may be more lethal in men, although its incidence in women is greater. A family history of porphyria was established in one case and was probable in two others.

Hepatic changes occurred in most cases and included congestion, centrolobular necrosis, and fatty degeneration; granules of iron-free lipochrome pigment were found in the hepatic cells of half of the patients. Pulmonary infarction had occurred in three cases. Neurogenic atrophy of the muscles with hyaline degeneration was present in almost half of the patients. Atrophy of the testes had occurred in all the patients who had symptomatic acute porphyria at the time of death.

Neuropathologic changes were found in the eight cases in which nerve tissue was available. Patchy demyelination and degeneration of the axis

Reprinted from the Canadian Medical Association Journal.

cylinders were present in the peripheral nerves, dorsal roots, cauda equina, and autonomic nervous system. Degeneration of nerve cells was found in the anterior-horn cells of the spinal cord, dorsal-root ganglia, cerebellum, dorsal nucleus of the vagus nerve, and the celiac plexus. Minor, nonspecific alterations were present in the cerebral cortex of half the patients who were free from associated diseases.